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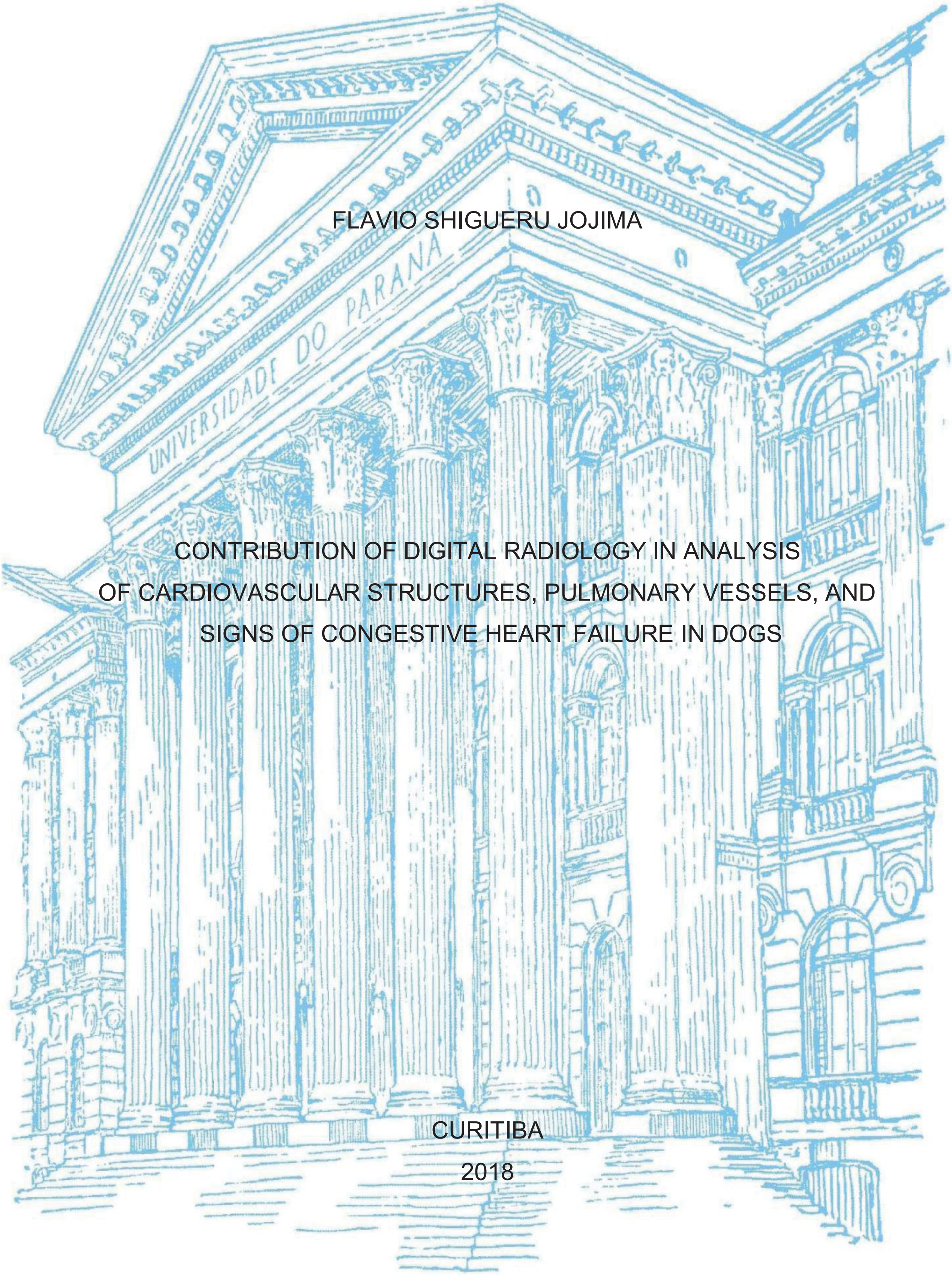

FLAVIO SHIGUERU JOJIMA

CONTRIBUTION OF DIGITAL RADIOLOGY IN ANALYSIS OF CARDIOVASCULAR STRUCTURES, PULMONARY VESSELS, AND SIGNS OF CONGESTIVE HEART FAILURE IN DOGS

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Tese apresentada ao Programa de Pós-graduação em Ciências Veterinárias, do Setor de Ciências Agrárias, da Universidade Federal do Paraná, como requisito parcial para obtenção do título de Doutor em Ciências Veterinárias.

Orientadora: Profª. Drª. Tilde Rodrigues Froes

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Os membros da Banca Examinadora designada pelo Colegiado do Programa de Pós-Graduação em CIÊNCIAS VETERINÁRIAS da Universidade Federal do Paraná foram convocados para realizar a arguição da tese de Doutorado de **FLAVIO SHIGUERU JOJIMA** intitulada: **Contribution of Digital Radiology in Analysis of Cardiovascular Structures, Pulmonary Vessels, and Signs of Congestive Heart Failure in Dogs**, após terem inquirido o aluno e realizado a avaliação do trabalho, são de parecer pela sua APROVAÇÃO no rito de defesa.

A outorga do título de doutor está sujeita à homologação pelo colegiado, ao atendimento de todas as indicações e correções solicitadas pela banca e ao pleno atendimento das demandas regimentais do Programa de Pós-Graduação.

CURITIBA, 11 de Dezembro de 2018.

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“Without dreams, life has no sparkle. Without goals, dreams have no foundation. Without priorities, dreams do not come true. Dream, set goals, set priorities, and take risks to fulfill your dreams. It is better to err by trying than to err by omitting!”

- Augusto Cury

RESUMO

O exame radiográfico torácico cardiovascular é recomendado em cães como parte do diagnóstico na análise de cães cardiopatas. Comparado com a ecocardiografia o exame radiográfico é amplamente difundido e apresenta menor custo. Apesar do exame Doppler ecocardiográfico ser considerado o padrão ouro, a técnica não está disponível em todos os locais e exige um operador treinado e com alto grau de experiência para a interpretação. As formas de se analisar a silhueta cardíaca pelo exame radiográfico compreendem-se na análise subjetiva e a técnicas de mensuração do coração pelos métodos “Vertebral Heart Scale” (VHS) e “Manubrium Heart Scale” (MHS). A análise radiográfica do sistema cardiovascular por completo ainda compreende a análise dos vasos pulmonares, mensuração destes vasos, a busca por sinais de insuficiência como a congestão venosa, presença do edema pulmonar cardiogênico ou efusão pleural. Os objetivos dessa tese compreendem em se determinar novas formas de se medir a silhueta cardíaca e vasos pulmonares em cães com doença mixomatosa da valva mitral (DMVM) pela radiografia e analisar o uso da telemedicina com ferramentas atuais digitais na busca precoce do diagnóstico do edema pulmonar cardiogênico em cães. O primeiro capítulo é um estudo observacional que determinou fórmulas para detecção pela radiografia torácica de sinais de aumento da pressão atrial esquerda em cães com DMVM. Verificou que as fórmulas com as medidas radiográficas adquiridas no estudo podem estimar as medidas ecocardiográficas de aumento de pressão no átrio esquerdo em cães com DMVM e com isso ajudar na decisão de iniciar o tratamento precoce desses pacientes. O segundo capítulo é um estudo interobservador com 79 casos de cães com e sem DMVM para testar a medida radiográfica da silhueta cardíaca e região de átrio esquerdo pela técnica do MHS comparando-se aos dados ecocardiográficos. No estudo, as medidas de eixo longo, eixo curto, átrio esquerdo (AE) e manúbrio (M) foram consideradas quase perfeitas no teste de correlação intraclasse (ICC). As medidas de *short-MHS*, *long-MHS*, *LAs-MHS* e *overall-MHS* apresentaram bons resultados de correlação intraclasse. Os valores de corte para o *overall-MHS* foram de 5,97 e para os *LAs-MHS* foi de 1,13. O uso de *overall-MHS* e *LAs-MHS* para a avaliação da cardiomegalia em cães de raças pequenas é uma ferramenta importante para o uso no dia-a-dia. O terceiro capítulo é um estudo observacional que verificou a precisão de um radiologista e cardiologista veterinários experientes na detecção de edema pulmonar cardiogênico usando o smartphone como ferramenta de visualização. Observou-se que não houve diferença entre os observadores na detecção de edema por meio de smartphone, obtendo-se boa acurácia na detecção de casos com edema pulmonar cardiogênico, indicando que a ferramenta de telemedicina pode ser útil em situações de emergência em que tanto o radiologista quanto o cardiologista não estejam disponíveis para visualização imediata no computador.

Palavras-chave: Radiografia torácica. Pressão média do átrio esquerdo. *MHS*. ICC. DMVM.

ABSTRACT

The thoracic radiographic cardiovascular examination is recommended as part of the diagnosis in dogs with heart disease. Compared to echocardiographic examination, the radiographic examination is widely diffused and presents a lower cost. Despite the fact that the Doppler echocardiographic examination be considered the gold standard, the technique is not available in all locations and requires a trained operator and with a high degree of expertise to the interpretation. The ways to parse the cardiac silhouette by radiographic examination comprise on subjective analysis and measurement techniques of the heart by methods “Vertebral Heart Scale” (VHS) and “Manubrium Heart Scale” (MHS). The radiographic examination of the cardiovascular system by fully understand the analysis of pulmonary vessels, measurement of these vessels, the search for signs of inadequacy as the venous congestion, presence of cardiogenic pulmonary edema or pleural effusion. The aims of this thesis include determining new ways to measure the cardiac silhouette and pulmonary vessels in dogs with myxomatous mitral valve disease (MMVD) by x-ray and examine the use of telemedicine with current digital tools in early search in seeking diagnosis early cardiogenic pulmonary edema in dogs. The first chapter is an observational study that determined formulas for detection by thorax x-ray signs of left atrial pressure in dogs with MMVD. It was found that the formulas with radiographic measurements acquired in the study can estimate the measures echocardiographic findings of increased pressure in the left atrium in dogs with MMVD and help in the decision to start early treatment of these patients. The second chapter is a interobserver study with 79 cases of dogs with and without MMVD to test the radiographic measurement of cardiac silhouette and region of left atrium by MHS technique compared to the echocardiographic data. In the study, measurements of the long axis, short axis, left atrium (LAs) and manubrium (M) were considered almost perfect in the intraclass correlation (ICC) test. The short-MHS, long-MHS, LAs-MHS and overall-MHS measures showed good intraclass correlation results. Cut-off values for overall-MHS were 5.97, and for LAs-MHS it was 1.13. The use of overall-MHS and LAs-MHS for the evaluation of cardiomegaly in small breed dogs is an important tool for day-to-day use. The third chapter is an observational study that verified the accuracy of an experienced veterinarian radiologist and cardiologist in the detection of cardiogenic pulmonary edema using the smartphone as a visualization tool. It was observed that there was no difference between the observers in the detection of edema through smartphone, obtaining a good accuracy in the detection of cases with cardiogenic pulmonary edema, indicating that telemedicine tool can be useful in emergencies situations in which both the radiologist and the cardiologist are not available for immediate viewing on the computer.

Keywords: Thoracic radiographs. Mean left atrium pressure. MHS. CHF. MMVD.

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LIST OF ABBREVIATIONS AND ACRONYMS

ACVIM	- American College of Veterinary Internal Medicine
Ao	- Aorta
AUC	- Area under the curve
CHF	- Congestive Heart Failure
CVC	- Caudal Vena Cava
DICOM	- Digital Imaging and Communications in Medicine
et al	- and others
ICC	- Intraclass correlation test
IRVT	- Isovolumetric Velocity Time
JPEG	- Joint Photographic Expert Group
kV	- Kilovoltz
LA	- Left Atrium
LABL	- Left Atrium Bisection Line
LA-VHS	- Long Axis of VHS
LS	- Left Side
LVIDDN	- Normalized left ventricular internal diameter in diastole
mA	- Milliampere
MHS	- Manubrium cardiac score
MHz	- Megahertz
MLAP	- Mean left atrium pressure
MMVD	- Myxomatous Mitral Valve Disease
ROC	- Receiver operating characteristics
RS	- Right Side

SA-VHS	- Short Axis of VHS
T4	- Fourth thoracic vertebra
VHS	- Vertebral Heart Score
VLAS	- Vertebral left atrium score

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1. CHAPTER 1- USE OF MEASUREMENTS FROM THORACIC RADIOGRAPHS TO IDENTIFY HIGH MEAN LEFT ATRIUM PRESSURE IN DOGS WITH MYXOMATOUS MITRAL VALVE DISEASE.

ABSTRACT

The aim of this study was to estimate echocardiographic elevated mean left atrium pressure (MLAP) based on measurements from thoracic radiographs and to determine a cut-off value for each radiographic measurement that suggests a high MLAP. A retrospective cross-sectional study was performed to include cases admitted from January 2015 to December 2016. Thoracic radiographic examinations from 93 dogs with and without a high MLAP were included. Specific measurements were made from thoracic radiographs and compared with echocardiographic variables known to indicate high MLAP. This comparison was used to generate equations that allowed the estimation of echocardiographic surrogates from the radiographic measurements. The values indicative of high MLAP were obtained using a regression curve. Formulas that indicated high MLAP were generated using a number of radiographic measurements. Positive echocardiographic findings of high MLAP were used as the gold standard. These formulas helped to predict high MLAP in myxomatous mitral valve disease (MMVD) without the need for echocardiographic examination. The best formula was left atrium (LA):aorta $(Ao)_{echo}$ = 0.03×(vertebral heart score,(VHS)) + 0.14×(LA) + 0.27×(LA:caudal vena cava $(CVC)_{rad}$). Values ≥12.2v for VHS, ≥4.5cm for LA, ≥3.3 for $LA{:}Ao_{rad}$ and ≥3.2 for $LA{:}CVC_{rad}$ suggested high MLAP. Thus, we propose equations, based on measurements from thoracic radiographs, to identify high MLAP. Simple radiographic thoracic measurements, such as $LA{:}CVC_{rad}$, can be used to define overload and a high MLAP in dogs with MMVD.

Keywords: LA:Ao, left atrium enlargement, pulmonary venous enlargement, thoracic radiography, VHS

USO DE MEDIDAS NA RADIOGRAFIAS TORÁCICAS PARA IDENTIFICAR A PRESSÃO MÉDIA ATRIAL ESQUERDA ALTA EM CÃES COM DOENÇA DE VALVA MITRAL MYXOMATOUS.

RESUMO

O objetivo desse estudo foi estimar a pressão média do átrio esquerdo (PMAE) elevada observada na ecocardiografia com base em medidas de radiografias torácicas e determinar um valor de corte para cada medida radiográfica que sugere um aumento da PMAE. Um estudo transversal retrospectivo foi realizado com os casos admitidos de janeiro de 2015 a dezembro de 2016. Foram incluídos exames radiográficos torácicos de 93 cães com e sem PMAE aumentada. As medidas específicas foram realizadas a partir de radiografias torácicas e comparadas com variáveis ecocardiográficas conhecidas por indicarem alta PMAE. Essa comparação foi utilizada para gerar equações que permitiram estimar os índices ecocardiográficos a partir das medidas radiográficas. Os valores indicativos de alta PMAE foram obtidos utilizando uma curva de regressão. As fórmulas que indicaram alta PMAE foram geradas usando um número de medidas radiográficas. Os achados ecocardiográficos positivos de alta PMAE foram utilizados como padrão-ouro. Essas fórmulas ajudaram a prever alta PMAE na doença valvar mitral mixomatosa (DMVM) sem a necessidade de exame ecocardiográfico. A melhor fórmula foi o átrio esquerdo (AE): aorta $(Ao)_{echo} = 0,03 \times$ (escore cardíaco vertebral, (VHS)) + 0,14 × (AE) + 0,27 × (AE: veia cava caudal $(VCC)_{rad}$). Valores ≥12,2v para VHS, ≥4,5cm para LA, ≥3,3 para $LA{:}Ao_{rad}$ e ≥3,2 para $LA{:}VCC_{rad}$ sugeriram alta PMAE. Assim, propomos equações, baseadas em medidas de radiografias torácicas, para identificar alta PMAE. As medidas de radiografia torácica simples, como $LA{:}VCC_{rad}$, podem ser usadas para definir sobrecarga e uma alta PMAE em cães com DMVM.

Palavras-chave: AE:Ao, aumento do átrio esquerdo, congestão venosa pulmonar, radiografia torácica, VHS.

1.1 INTRODUCTION

Myxomatous mitral valve disease (MMVD) is the most common heart disease in dogs (WARE, 2014). MMVD is diagnosed on the basis of clinical signs, and echocardiographic and thoracic radiographic examination, but the sensitivity and accuracy of each parameter varies (ABBOTT, 2008; MATTIN et al., 2015). Despite some limitations, thoracic radiography is considered the best screening test to identify signs of left congestive heart failure (CHF), through the demonstration of venous congestion and cardiogenic pulmonary edema (ABBOTT, 2008).

Echocardiographic examination is considered the gold standard for the diagnosis of MMVD and allows for the structural and functional evaluation of the heart, early detection of disease and classification of the stage of heart failure according to the American College of Veterinary Internal Medicine (ACVIM) Specialty of Cardiology consensus panel (ATKINS et al., 2009; OYAMA et al., 2004; SCHOBER et al., 2010a). Undoubtedly, echocardiography is the most accessible diagnostic method for the detection of a high mean left atrial pressure (MLAP). The echocardiographic parameters that allow the sonographic diagnosis of high MLAP are: left atrium to aorta ratio ($LA:Ao_{echo}$), wave E, the E:isovolumetric relaxation time (IVRT) ratio and the wave E:E' ratio (KIM; PARK, 2015; OYAMA et al., 2004; SCHOBER et al., 2010a). However, treatment in dogs with MMVD should be commenced once they have reached stage B2 and have $LA:Ao_{echo}$>1.6, a vertebral heart score (VHS) >10.9 and a normalized left ventricular internal diameter in diastole (LVIDDN) >1.7 (BOSWOOD et al., 2016).

Despite the advantages of echocardiography, it is a subjective technique, and the accuracy of the examination is highly correlated to the experience of the examiner (ABBOTT, 2008). Additionally, data analysis can be time-consuming and, in emergencies, such as pulmonary edema, this can be a limiting factor. In dyspneic patients, a thoracic radiographic examination can again be a useful screening technique. Radiographic examination is faster to perform and simpler for non-specialists to interpret (BAHR, 2013).

The measurement of the size of the cardiac silhouette on radiographic examination is also subjective. Findings indicating CHF include pulmonary edema and pleural effusion, as well as signs of venous congestion (BAHR, 2013). Pulmonary venous congestion can be identified by radiographic examination when there is an increase in the diameter of the cranial pulmonary veins compared to the corresponding pulmonary artery in the left radiographic projection, or by comparison of the caudal pulmonary vein with the diameter of the ninth rib on the right side on the dorsoventral projection (THRALL; LOSONSKY, 1976).

A less subjective way of assessing the size of the cardiac silhouette by radiographic examination is the vertebral heart score (BUCHANAN; BÜCHELER, 1995). VHS values between 9.7 and 10.7 were initially considered normal in dogs; however, later studies identified different values in certain breeds, where normal VHS can be up to 10.5v for Cavalier King Charles Spaniels and German Spitz, up to 10.2v for Beagles, up to 10.6v for Greyhounds, up to 10.7v for Pugs, up to 12.1v for Bulldogs, up to 11.0v for Whippets and up to 11.4v for Boston Terriers (BAVEGEMS et al., 2005; HANSSON et al., 2005; JEPSEN-GRANT; POLLARD; JOHNSON, 2013; KRAETSCHMER et al., 2008; MARIN et al., 2007). This measurement technique is relatively poor at detecting specific individual cardiac chamber enlargements, where measurement may be within normal limits, even in patients with enlarged cardiac silhouettes (BUCHANAN; BÜCHELER, 1995).

Based on the difficulties in the analysis and use of the VHS, some researchers have proposed a specific method of measuring the left atrium by radiographic examination, to be applied in patients with MMVD (SANCHEZ et al., 2013). This method combines the use of the VHS with the measurement of the left atrium with reference to the intersection point of the VHS. First, a measurement is made from the point of intersection of the short and long heart axis to the caudal edge of the short axis (SA-VHS), then, starting from the same point, a measurement is made up to the dorsal edge of the long axis (LA-VHS), and these two measurements are summed. In addition, a line is drawn from the midpoint of the intersection of the long and short axis of the VHS to the dorsal border of the left atrium (SANCHEZ et al., 2013). Using this method, it is possible to detect focal cardiac enlargement, especially in the left atrium, which often occurs in MMVD. The study authors also proposed other measurements, however, the study included only a few cases (SANCHEZ et al., 2013). The VHS and measurements of the left atrium are unable to identify high MLAP in patients with MMVD.

In this study, we hypothesized that a new method for radiographic measurement of the left atrium, specifically for use in patients with MMVD, could produce an equation for the diagnosis of high MLAP, without the need for echocardiographic examination. We aimed to correlate measurements from thoracic radiographs with echocardiographic measurements to grade the severity of disease and detect cases with a high MLAP. Therefore, the aims of this study were four-fold: 1) to propose an equation based on measurements from thoracic radiographs to estimate the presence of high MLAP, as detected by echocardiography; 2) to confirm the effectiveness of the measurements in the radiographic examination in patients with MMVD; 3) to compare the measurements from the radiographic examination with the measurements from the echocardiographic examination; and 4) to determine a limit for each radiographic measurement that suggests high MLAP.

1.2 MATERIALS AND METHODS

A retrospective, observational, cross-sectional study was conducted using data from dogs admitted to a veterinary teaching hospital, in which thoracic radiographs and echocardiographic examinations had been performed between January 2015 and December 2016.

Inclusion criteria were: patients had echocardiographic and radiographic examinations, dogs were less than 15kg or were a small breed, and dogs did not receive pimobendan before the examinations.

Exclusion criteria were: no echocardiographic measurements of the $LA{:}Ao_{echo}$, mitral E wave, IRVT or E:IRVT ratio, cases with significant additional radiographic findings, such as severe pulmonary edema and pleural effusion, or insufficient radiographic quality to allow measurements.

Echocardiographic examinations

Reports of the echocardiographic exams were obtained from the database of the Laboratory of Comparative Cardiology. All examinations were performed with either a Mylab 30 Gold Vet (ESAOTE, Italy), with 1–4 MHz and 5–10 MHz sector transducers, or a Philips Affiniti 50 (PHILIPS, USA), with 2–4MHz and 3–8MHz transducers, selected according to the size of the patient. Echocardiographic examinations were performed according to published guidelines (BOON, 2011).

Radiographic evaluations

Thoracic radiographs were obtained from the database of the Diagnostic Imaging Laboratory in DICOM format. The initial examinations were performed on a

Medicor Budapest X-ray device (Neo-Diagnomax) with a power of 500 mA; later an AGFA model CR-30X (AGFA HealthCare NV, Belgium) was used.

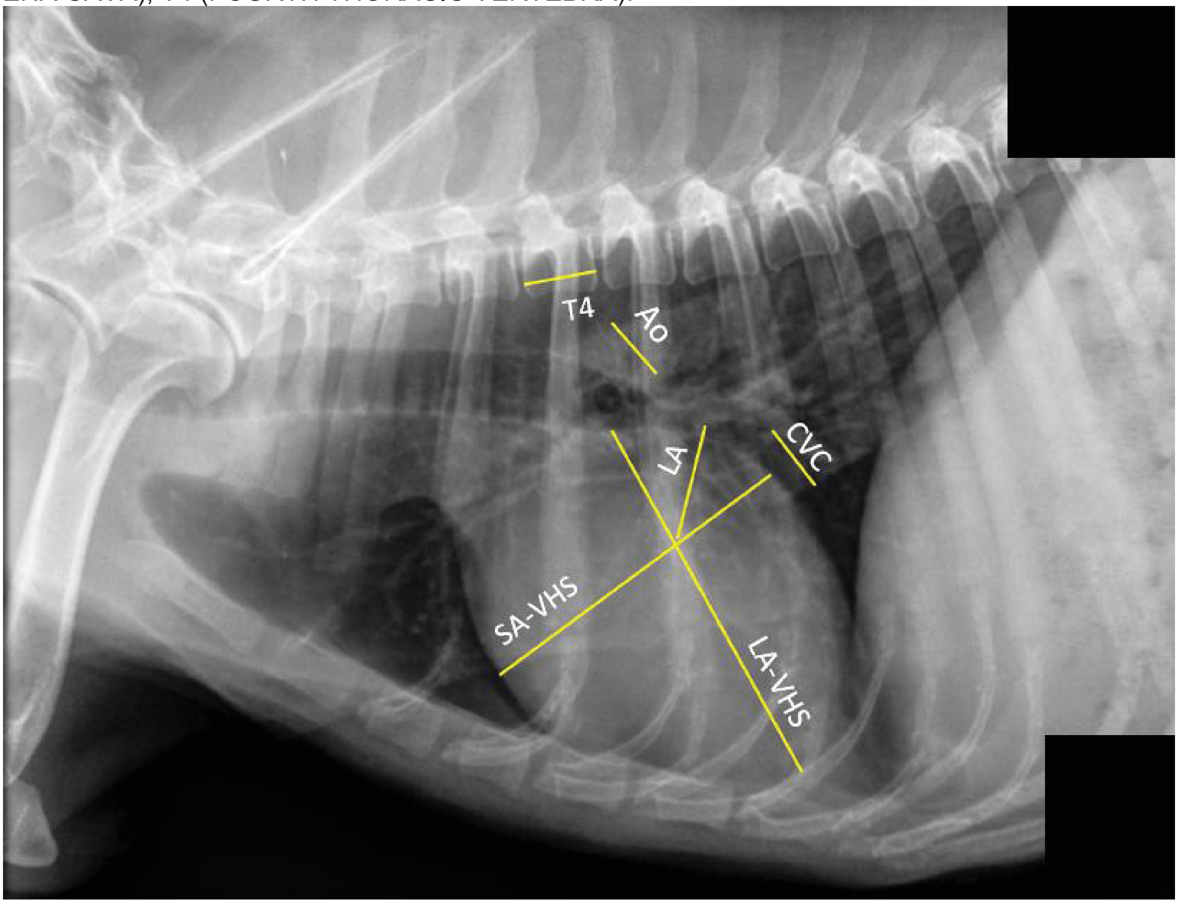
Evaluations were made by a trained radiologist using Radiant DICOM Viewer 3.4.2® (Posnania, Poland, 2016). The following measurements were made from the thoracic radiographs: VHS, LA size, vertebral left atrium score (VLAS), aorta width (Ao), caudal vena cava (CVC) and the size of the fourth thoracic vertebra (T4) (Figure 1.1).

VHS was measured according to Buchanan and Bücheler (1995), with the changes proposed by Hansson et al. (2005) to standardize the obtained values. The long axis of VHS (LA-VHS) was measured as the distance from the ventral part of the carina to the apex of the heart. The value for the short axis of VHS (SA-VHS) was obtained using the caudal border of the heart at the midpoint of the entry of the caudal vena cava as a reference. Then, a line was drawn from the previously described point (cardiac edge versus caudal vena cava) to the cranial cardiac border, perpendicular to the LA-VHS line (HANSSON et al., 2005). The VHS was calculated according to Buchanan and Bücheler (1995), with only the SA-VHS measurement being made according to Hansson et al. (2005).

The LA size was obtained by measuring the length of a new line drawn at 45 degrees from the intersection of the LA-VHS and SA-VHS and the most dorsocaudal portion of the cardiac border. This value was compared to the length of the thoracic vertebral bodies, with the measurement starting from the fourth thoracic vertebra. This measurement was labeled the vertebral left atrial score (VLAS) (BUCHANAN; BÜCHELER, 1995).

The radiographic silhouette of the dorsal and ventral border of each vessel was used to obtain the width of the aorta and the CVC. The measurement of the aorta was made caudal to the carina, and dorsocaudal to the base of the heart. The CVC was measured where the vessel overlapped with the caudal border of the heart (Figure 1.1). The length of the fourth thoracic vertebra was measured between the cranial and caudal articular joint edges of the vertebra in its body portion. All measurements were made in both right and left lateral projections (Figure 1.1).

FIGURE 1.1 RIGHT LATERAL THORACIC RADIOGRAPH SHOWING THE MEASUREMENTS MADE FOR THE STUDY. SA-VHS (SHORT AXIS OF THE VERTEBRAL CARDIAC SCORE), LA-VHS (LONG AXIS OF THE VERTEBRAL CARDIAC SCORE), LA (LEFT ATRIUM), AO (AORTA), CVC (CAUDAL VENA CAVA), T4 (FOURTH THORACIC VERTEBRA).



The relationships between the left atrium and the aorta ($LA{:}Ao_{rad}$), the left atrium and the CVC ($LA{:}CVC_{rad}$) and the left atrium and the fourth thoracic vertebra ($LA{:}T4_{rad}$) were later calculated and tabulated in a Microsoft Office Excel worksheet 2016 for Windows (Redmond, WA, USA). The information from each patient, as well as the echocardiographic measurements obtained from the echocardiographic reports, were entered in the same Excel table for later analysis.

Statistical analysis

Statistical analysis was performed to establish a reliable parameter from the radiographic examination to detect signs of congestion in patients with heart disease. Initially, all echocardiographic and radiographic measurements were submitted to a Bayesian analysis. The response variables (Yi) followed a normal distribution; that is, Yi ~ Normal (μi, σi2), i = 1, 2, ..., nj for the jth treatments. For each μi and σi2, non-informative distributions were considered, respectively, mi ~ Normal (0,10-6) and ti ~ Gamma (10-3,10-3) (σ2 = t-1, OpenBugs parameterization). Multiple comparisons were made between the posteriori distributions of the average. At the 5% level of significance, the treatments whose 95% confidence intervals (ICr) for the mean differences were considered different if they did not include a value of zero. The means and confidence intervals for all the parameters were calculated using the BRugs package of the program R (R DEVELOPMENT CORE TEAM).

A total of 220,000 values were generated in a MCMC (Markov chain Monte Carlo) process, with a sampling period of 20,000 initial values. In the collection of values, a skip of 20 cycles was used for each sample, so the final sample included 10,000 values. Convergence of the chains was verified through the CODA package of R, according to Heidelberger and Welch (1983) and Geweke (1992).

Pearson's correlation coefficients were used to verify the degree of correlation between radiographic and echocardiographic measurements that were directly related to congestion. For this, comparisons of each echocardiographic index with each radiographic value were made to establish the degree of the relationship between them. Pearson's correlation coefficients were also used to verify intra- and inter-observer correlation of the radiographic measurements performed in the study (Table 1.1). To analyze this relationship, the following indices were used for this analysis: a r value from -1.0 to -0.7: strong negative correlation; from -0.7 to -0.3: negative correlation; from -0.3 to +0.3: small correlation or no association; from +0.3 to +0.7: weak positive correlation; from +0.7 to +1.0: strong positive correlation.

The data were analyzed statistically to identify variables with a significant influence on a high MLAP, using the "stepwise" methodology of SAS statistical software; this allows for the elimination of variables that do not have a significant influence on the variable in question. An equation was derived to predict the $LA:Ao_{echo}$, mitral E wave, E:IRVT and E:E' in an echocardiograph based on the variables that had a significant influence on these parameters.

The regression curves were constructed using the echocardiographic measure of a high MLAP as an independent variable and the radiographic variables as dependent variables. Only the radiographic measurements of the right side (RS) were used in the formulas presented in Table 1.2. For the $LA:Ao_{echo}$ ratio in the echocardiograph, the regression curves were built with the VHS, LA, $LA:Ao_{rad}$ and $LA:CVC_{rad}$ radiographic measurements.

All statistical analyses were selected and performed by two authors (F.S.J; A.L.S.). The data were collected and analyzed using Microsoft Office Excel (Microsoft Office 2016 for Windows, Redmond, WA, USA), R for Windows (Version 3.1.1 Ri386, R Foundation for Statistical Computing, Vienna, Austria, 2014) and SAS (Version 9.4, SAS Institute Inc., Cary, NC, USA, 2016).

1.3 RESULTS AND DISCUSSION

The study included 158 thoracic radiographic examinations. Sixty-six radiographs were excluded as they were unsuitable for cardiac measurements due to poor quality and the presence of pleural effusion or a significant pulmonary edema. Of the remaining 93 cases, 60 were females and 33 males. There was no statistically significant difference between females and males in any of the measured echocardiographic and radiographic variables. The median dog weight was 9.3kg, with minimum and maximum values of 2.0 and 18.8kg. The median age of the dogs was 11.0 years, ranging from 1.5 to 18.0 years; in only one case, the owner did not know the correct age of the patient. Many patients were mixed breed dogs (26 dogs), but the other patients were: 16 Beagles, 10 Pinschers, seven Cocker Spaniels, seven Dachshunds, seven Poodles, seven Schnauzers, six Lhasa Apsos, two Malteses, two Whippets, and one case each of a Brazilian Terrier, a Fox Terrier and a Yorkshire Terrier.

Upon investigation of the Pearson correlation coefficients, we observed that the variables obtained in the right radiographic projection were slightly higher than those obtained from the left. Table 1.1 presents the Pearson correlation coefficients of the radiographic and echocardiographic measurements. The correlations between the echocardiographic variable $LA:Ao_{echo}$ and the radiographic variables of the right side LA, VLAS, $LA:Ao_{rad}$, $LA:CVC_{rad}$ and $LA:T4_{rad}$ and of the echocardiographic variable E wave with the right side LA, VLAS and LA:T4rad and the left side (LS) VLAS were strong and positive. Except for the correlation of the E:E' echocardiographic variable with the VHS-right and left radiographic variables; LA – right and left, VLAS – left, $LA:Ao_{rad}$ – right and left and $LA:T4_{rad}$ – right and left, which were considered null associations or had small correlations, all other correlations were considered weak and positive associations.

TABLE 1.1. PEARSON'S CORRELATION TEST R VALUES, USING ECHOCARDIOGRAPHIC MEASURES THAT SUGGEST HIGH MLAP, IN COMPARISON TO THE RADIOGRAPHIC MEASURES TESTED.

Radiographic variables	Echocardiographic Variable							
	LA:Ao		E wave		E:IVRT		E:E'	
	RS	LS	RS	LS	RS	LS	RS	LS
VHS	0.60**	0.59**	0.68**	0.68**	0.51**	0.52**	0.21^{ns}	0.21^{ns}
LA	0.73**	0.60**	0.71**	0.66**	0.53**	0.50**	0.18^{ns}	0.14^{ns}
VLAS	0.72**	0.69**	0.70**	0.71**	0.53**	0.58**	0.30*	0.27*
LA:Ao	0.74**	0.52**	0.68**	0.59**	0.45**	0.41**	0.29*	0.20^{ns}
LA:CVC	0.75**	0.47**	0.66**	0.47**	0.55**	0.40**	0.34**	0.31*
LA:T4	0.72**	0.52**	0.71**	0.57**	0.56**	0.47**	0.29*	0.26*

^{Ns} Not significant p≥0.05.
* Significant at p≤0.05.
** Significant at p≤0.01.
RS: Right side; LS: Left side; VHS: Vertebral Heart Score; VLAS: Vertebral Left Atrial Score; LA: Left Atrium; LA:Ao: Left atrium to Aorta ratio; LA:CVC: Left atrium to caudal vena cava ratio; LA:T4: Left atrium to 4th thoracic vertebra; E:IVRT: E wave to Isovolumetric relation time ratio; E:E': E wave to E' wave ratio.

To date, a few studies have compared the measurement of echocardiographic variables with single radiographic measurements (HERNANDEZ-LOPEZ; MACHEN; OYAMA, 2012; SANCHEZ et al., 2013), but single radiographic measurements have always been found to be an inferior method of diagnosis of a high MLAP. The Pearson correlation coefficient shows that the $LA:Ao_{rad}$ ratio had an r of 0.74 with the $LA:Ao_{echo}$ ratio, whereas the equation generated in this study that estimated $LA:Ao_{echo}$ using the variables VHS, LA and $LA:CVC_{rad}$ (Table 1.2) had an R2 of 0.97, indicating that it is better than a single measurement for estimating high MLAP from a radiographic examination.

In the literature, the $LA:Ao_{echo}$ ratio from echocardiograms and the left atrium bisection line (LABL) are weakly correlated, contrasting with the strong correlation observed in this study (HERNANDEZ-LOPEZ; MACHEN; OYAMA, 2012). In another study, the r value for the Pearson correlation was similar to that found in our study (0.79 and 0.74) (SANCHEZ et al., 2013). There are no correlation studies using other echocardiographic measures of high MLAP. However, we obtained formulas that can estimate the echocardiographic E wave, E:IVRT and E:E’ variables based on radiographic measurements. This will assist in clinical decision-making with respect to the use of medications to decrease these measurements and, consequently, the congestion. The most commonly used variable to assess high MLAP on echocardiography is $LA:Ao_{echo}$, however, if measurement of this ratio proves inconclusive, other echocardiographic measurements can be made to confirm a diagnosis.

The stepwise methodology used to acquire the formulas included the radiographic parameters that best correlated with echocardiographic high MLAP and discarded the least important parameters. In this process, the best parameters are selected in the first step, and consequently have a greater impact on the respective variable. The best variable for estimation of high MLAP by radiographic examination, based on the echocardiographic parameter $LA:Ao_{echo}$, was $LA:CVC_{rad}$. The estimation using $LA:CVC_{rad}$ multiplied by 0.52938 gave an R2 of 0.96. The radiographic measurements that best predicted echocardiographic measurements of high MLAP were LA for E wave and E:IVRT (multiplied by 28.32 and 0.76, giving an R2 of 0.91 and 0.61, respectively) and VHS for E:E' (multiplied by 0.98, giving an R2 of 0.91).

In left lateral radiographs, VLAS alone was able to predict the $LA:Ao_{echo}$ ratio, E wave and the E:IVRT ratio (when multiplied by 0.59, 38.90 and 1.04, respectively) with R2 values of 0.95, 0.91 and 0.60, respectively. For the estimation of the E:E' ratio, VHS was used and multiplied by 1.007, leading to an R2 of 0.91.

The formulas that best predicted echocardiographic high MLAP variables by the stepwise method are shown in Table 1.2, where it can be seen that more than one radiographic measurement was used to produce the formulas. The formulas derived from values from the right lateral projection were slightly superior when compared to the left side values. The coefficient of determination (R2) was the lowest for the E:IVRT ratio, among all predictors of high MLAP. The equation that estimated the $LA:Ao_{echo}$ ratio based on echocardiography using the radiographic measurements from the right lateral projection had the highest R2.

TABLE 1.2. FORMULAS TO ESTIMATE THE ECHOCARDIOGRAPHIC VARIABLES USING THE RADIOGRAPHIC MEASUREMENTS OBTAINED.

Estimated variable	Radiography	Equation	R^2	C
LA:Ao	Right	y=0.03*(VHS)+0.14*(LA)+0.27*(LA:CVC)	0.97	5.43
	Left	y=0.03*(VHS)+0.16*(LA)+0.46*(VLAS)+0.13*(LA:CVC) -0.36*LA:T4)	0.96	4.56
E wave	Right	y=16.89*(LA)+14.88*(LA:Ao)	0.92	-1.38
	Left	y=18.16*(LA)+37.48*(VLAS)+11.25*(LA:Ao)-34.31*(LA:T4)	0.92	4.15
E:IVRT	Right	y=0.76*(LA)	0.61	9.69
	Left	y=-0.31*(VHS)+2.43*(VLAS)	0.64	1.46
E:E'	Right	y=0.60*(VHS)+1.61*(LA:CVC)	0.92	-0.22
	Left	y=0.60*(VHS)+1.63*(LA:CVC)	0.92	-0.34

VHS: Vertebral Heart Score; VLAS: Vertebral Left Atrial Score; LA: Left Atrium; LA:Ao: Left atrium to Aorta ratio; LA:CVC: Left atrium to caudal vena cava ratio; LA:T4: Left atrium to 4^{th} thoracic vertebra; E:IVRT: E wave to Isovolumetric relation time ratio; E:E': E wave to E' wave ratio.

The formulas obtained using the radiographic measurements from right lateral projections were more accurate than those obtained from the left side, as shown in Table 1.2. The variables that best estimated a high MLAP based on radiographic examination were $LA:CVC_{rad}$ for $LA:Ao_{echo}$, LA for E wave and E:IVRT and VHS for E:E'. Although it is possible to use a single radiographic variable to estimate the echocardiographic measurements that indicate a high MLAP, errors are reduced by cross-checking with multiple variables.

Diagnostic cut-off values for the radiographic variables can be derived by drawing a line on their regression curves, corresponding to the cut-off values for each echocardiographic variable, and recording where they cross. For example, if a patient with high MLAP disease has a minimum $LA:Ao_{echo}$ value of 1.6, the cut-off values, corresponding to where the regression line crosses this number, for the radiographic variables VHS, LA and $LA:CVC_{rad}$ are approximately 12.2v, 4.2cm and 3.2, respectively (Figure 1.2).

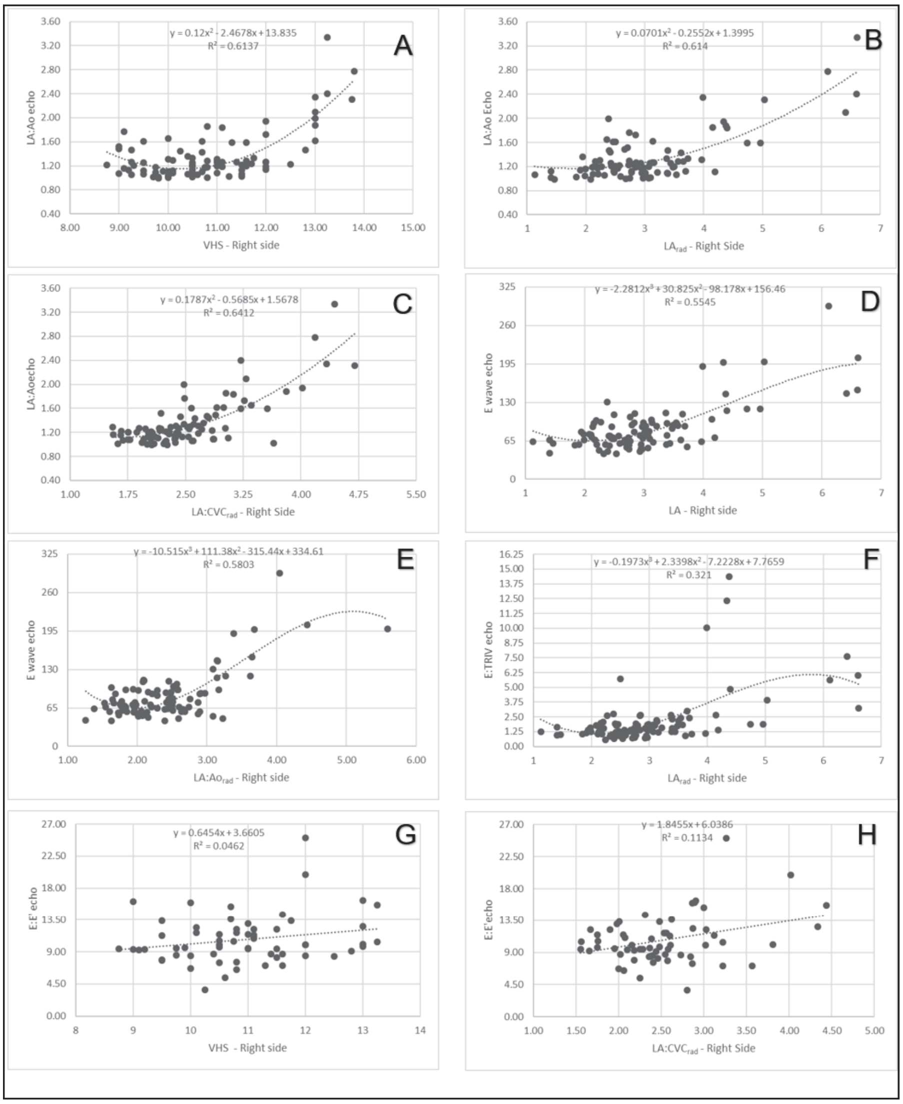
Cut-off values that suggest a high MLAP were also recorded for other echocardiographic variables, i.e. 130cm/s for the E wave, an E:IVRT ratio of 2.5 and an E:E' ratio of 9.0. For these variables, values that indicated high MLAP based on radiographic measurements were: for E wave, 4.5cm for the LA and a $LA:Ao_{rad}$ ratio of 3.3; for the E:IVRT ratio, an LA of 3.5cm, and for the E:E' ratio, a VHS limit of 8.8v and a $LA:CVC_{rad}$ ratio of 1.6 (Figure 1.2).

In the literature, the cited maximum values of VHS in normal dogs are 10.5v, although there are some breed variations outside this range (BAVEGEMS et al., 2005; BUCHANAN; BÜCHELER, 1995; HANSSON et al., 2005; JEPSEN-GRANT; POLLARD; JOHNSON, 2013; KRAETSCHMER et al., 2008; MARIN et al., 2007). According to our results, if a patient with MMVD has a VHS above 12.2v, high MLAP is present, as well as cardiomegaly. It is interesting to note that VHS values may vary in relation to the breed of the dogs, however, as MMVD occurs more commonly in small dogs, a cut value of 12.2v is a useful tool in the specific analysis of these patients, mainly in the detection of cardiac volume overload.

In studies evaluating the VHS, measurements obtained from the right lateral projection of the thorax were found to be better at detecting cardiac enlargement than those performed on the left lateral projection (GRECO et al., 2008). We also found the VHS to be larger on the right lateral thoracic projection, however, unlike in other studies, when we correlated this with echocardiographic measures of high MLAP, right lateral projection measures had higher Pearson correlation coefficients than left measures. This superiority was observed not only in the VHS, but in all measurements performed on the right side compared to the left side. The left lateral projection is generally considered better for evaluation of the cranial pulmonary vessels (BAHR, 2013). In general, this supports the view of other authors (BAHR, 2013) that at least three radiographic projections should be performed.

This study proposes a new approach for radiographic assessment of high MLAP without the need for echocardiography. Using the echocardiographic cut-off values for the definition of left heart volume overload, we verified that it is possible to identify a patient in overload via radiographic examination using a mathematical formula. Formulas are shown in Table 1.2; higher R2 values, when compared to the simple correlations presented in Table 1.1, indicate that the formulas are more accurate for the detection of volume overload.

FIGURE 1.2. REGRESSION GRAPHS WITH THE RADIOGRAPHIC MEASUREMENTS THAT WERE USED IN THE ESTIMATION EQUATION OF THE LA:AO$_{ECHO}$, E WAVE, E:IVRT AND E:E' RATIO IN ECHOCARDIOGRAPHY. (A) POLYNOMIAL REGRESSION LINE OF ORDER 2 NOTING THE POSITIVE CORRELATION OF LA:AO$_{ECHO}$ WITH VHS. (B) POLYNOMIAL REGRESSION LINE OF ORDER 2 OBSERVING THE POSITIVE CORRELATION OF LA:AO$_{ECHO}$ WITH LA SIZE. (C) POLYNOMIAL REGRESSION LINE OF ORDER 2 DEMONSTRATING POSITIVE CORRELATION OF LA:AO$_{ECHO}$ WITH LA:CVC$_{RAD}$ RATIO ON RADIOGRAPHY. (D) POLYNOMIAL REGRESSION LINE OF ORDER 3 OBSERVING THE POSITIVE CORRELATION OF E WAVE WITH LA SIZE ON THE RADIOGRAPH. (E) POLYNOMIAL REGRESSION LINE OF ORDER 3 OF THE E WAVE FOR THE LA:AO$_{RAD}$. (F) POLYNOMIAL REGRESSION LINE OF ORDER 3 OF E:IVRT RATIO WITH LA SIZE. (G) REGRESSION LINE FROM E:E’ RATIO TO VHS. (H) REGRESSION LINE FROM E:E’ RATIO TO LA:CVC$_{RAD}$.



An intra- and inter-observer repeatability analysis was performed with 15 randomly selected cases, and the data was evaluated using Pearson's correlation coefficients. In the intra-observer analysis, strong correlations were: LA-VHS RS (0.99), SA-VHS RS (0.99), LA RS (0.90), CVC RS (0.80), T4 RS (0.93), VHS LS (0.98), LA LS (0.94), Ao LS (0.81), CVC LS (0.96), T4 LS (0.91), VHS LS (0.98) and VLAS LS (0.90). In the inter-observer analysis, the correlations of the following measures were considered strong: LA-VHS RS (0.96), SA-VHS RS (0.99), LA RS (0.77), CVC RS (0.89), T4 RS (0.94), LA-VHS LS (0.97), LA LS (0.81), Ao LS (0.71), CVC LS (0.91), T4 LS (0.95) and VHS LS (0.94).

The inter- and intra-observer repeatability analysis demonstrated, through high Pearson's correlation coefficients, that these measures are highly reproducible. However, this study has a number of limitations. All measurements were performed by a single observer and the results require further validation of inter- and intra-observer repeatability. Only patients with suspected MMVD were selected for the radiographic measurements, so the formulas should only be applied to dogs with high MLAP and with this clinical profile. Because this was a retrospective study, it was not possible to establish which dogs were or were not treated with diuretics or vasodilators at the time of the thoracic radiography and echocardiographic examinations.

In summary, early signs of high MLAP in patients with heart disease can be detected in thoracic radiographs using the formulas produced in this study (Table 1.2). The use of these formulas provides a higher coefficient of determination than using individual radiographic measurements, and it is possible to use the cut-off values to identify signs of high MLAP and remodeling. The minimum values for each radiographic measurement that are indicative of high MLAP are: 12.2v for VHS, 4.5cm for LA, 3.3 for $LA:Ao_{rad}$ and 3.2 for $LA:CVC_{rad}$. This data will help clinicians diagnose high MLAP from radiographic examinations alone; this is of particular importance when an echocardiographic examination is not available or when the patient is not sufficiently stable to tolerate detailed and prolonged echocardiography.

We propose a number of equations using measurements taken from thoracic radiographs that can predict high MLAP in dogs with MMVD. In the future, these equations could be used in some form of computer or smartphone app. These measurements and correlations (e,g. $LA:CVC_{rad}$) can help to define high MLAP in patients with MMVD. High MLAP can be diagnosed from right lateral thoracic radiographs if any of the measured parameters are increased, namely: VHS ≥12.2v; LA ≥4.5cm; $LA:Ao_{rad}$ ≥3.3 and $LA:CVC_{rad}$ ≥3.2.

1.4 CONFLICT OF INTEREST:

The authors reports that the main author have a patent USO DE FÓRMULAS OBTIDAS A PARTIR DE MEDIDAS RADIOGRÁFICAS DO TÓRAX PARA IDENTIFICAR A CONGESTÃO VENOSA E PRE-EDEMA EM CÃES COM DOENÇA MIXOMATOSA DA VALVA MITRAL pending to Universidade Federal do Paraná at the process number BR 10 2017 023893 8.

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CHAPTER 2 - USE OF THORACIC RADIOGRAPHIC MHS MEASURE FOR DETECTION OF CARDIOMEGALY IN DOGS WITH MVMD.

ABSTRACT

Objective: The objectives of this study were to evaluate the MHS method in dogs with and without myxomatous mitral valve disease.

Animals: A retrospective cross-sectional study including cases admitted between January 2015 and December 2016. Thoracic radiographs from 79 dogs with and without Myxomatous Mitral Valve Disease were included.

Procedures: An interobserver study was performed and three observers with three different levels of experience performed the radiographic analyzes. The long and short axis of the heart, left atrium and manubrium were measured on lateral thoracic radiographs. Subsequently the following measurements were made: long-MHS, short-MHS, overall-MHS and LAs-MHS. The interobserver analyzes were submitted to the intraclass correlation test to evaluate the degree of agreement among the observers. ROC curves were generated to evaluate the accuracy of each method of radiological evaluation and Pearson´s correlation was used to evaluate the correlation between radiographic and echocardiographic measurements.

Results: In the inter-observer study, the long-axis, short-axis, left atrium (LA) and manubrium (M) measurements were considered almost perfect in the intraclass correlation test (ICC). The measurements of Short-MHS, Long-MHS, LAs-MHS and overall-MHS showed good intraclass correlation results. Cut-off value for the overall-MHS was 5.97 and for LAs-MHS was 1.13.

Conclusion and Clinical Significance: Radiographic assessment of overall-MHS and LAs-MHS for the evaluation of cardiomegaly in small breed dogs is an important tool for use in the clinic.

Keywords: Manubrium, Left atrium, Thoracic x-ray, LVIDDN, LA:Ao.

USO DA MEDIDA MHS NA RADIOGRAFIA PARA DETECÇÃO DE CARDIOMEGALIA EM CÃES COM DMVM.

RESUMO

Objetivo: Os objetivos deste estudo foram avaliar o método MHS em cães com e sem doença mitral mixomatosa.

Animais: Um estudo transversal retrospectivo incluindo casos admitidos entre janeiro de 2015 e dezembro de 2016 foi realizado. Foram incluídas radiografias torácicas de 79 cães com e sem doença da valva mitral mixomatosa.

Procedimentos: Um estudo interobservador foi realizado e três observadores com três diferentes níveis de experiência foram selecionados para realizar as análises radiográficas. O eixo longo e eixo curto do coração, átrio esquerdo e manúbrio foram medidos na radiografia do tórax lateral. Posteriormente, foram tomadas as seguintes medidas, tais como *long-MHS, short-MHS, overall-MHS e LAs-MHS*. A análise interobservador foi submetida ao teste de correlação intraclasse para avaliar o grau de concordância entre os observadores do estudo. Curvas ROC foram geradas para avaliar a acurácia de cada método de avaliação radiológica e a correlação de Pearson foi utilizada para avaliar a correlação entre as avaliações realizadas por medidas radiográficas e ecocardiográficas.

Resultados: No estudo interobservador, as medidas de eixo longo, eixo curto, átrio esquerdo (AE) e manúbrio (M) foram consideradas quase perfeitas no teste de correlação intraclasse (ICC). As medidas de *short-MHS*, *long-MHS*, *LAs-MHS* e *overall-MHS* apresentaram bons resultados de correlação intraclasse. Os valores de corte para o *overall-MHS* foram de 5,97 e para os *LAs-MHS* foi de 1,13.

Conclusão e significância clínica: O uso de medidas radiográficas de *overall-MHS e LAs-MHS* para a avaliação de cardiomegalia em cães de raças pequenas é uma ferramenta importante para o uso diário na rotina clínica.

Palavras-chave: Manúbrio, átrio esquerdo, radiografia de tórax, LVIDDN, AE:Ao.

2.1 INTRODUCION

Thoracic radiography is a complementary examination used to detect an enlarged cardiac silhouette and signs of congestive heart failure, such as venous congestion, pulmonary edema, pleural and pericardial effusion. It is considered a fast and non-invasive method (THRALL, 2018a). Cardiac size can be evaluated on radiographs subjectively or by using objective methods such as the "vertebral heart scale" (VHS). Changes in only one cardiac chamber may be visible as focal alterations of the heart size and shape but radiologic examination is not accurate for this (BAHR, 2018).

VHS is calculated as the relation of the length of the vertebrae from T4 with the transverse and longitudinal axes of the cardiac silhouette (BUCHANAN; BÜCHELER, 1995). Normal VHS values range from 9.5 to 12.2 depending on breed, size and thoracic conformation (BUCHANAN; BÜCHELER, 1995; HANSSON et al., 2005; JEPSEN-GRANT; POLLARD; JOHNSON, 2013; KRAETSCHMER et al., 2008; MARIN et al., 2007). This variation limits the use of this measurement. Additionally, changes in the spine and vertebrae may increase or decrease the vertebral length (v) and consequently affect interpretation. In a study of Bulldogs and Boston Terriers, median VHS values were of 12.1 and 11.4 in cases with no spinal abnormalities and 13.4 and 14.2 in cases where the dogs had spinal anomalies (JEPSEN-GRANT; POLLARD; JOHNSON, 2013; MOSTAFA; BERRY, 2017).

In an interobserver study with 16 evaluators with different degrees of experience, a variation of 1.0 ± 0.3 was observed in VHS in patients with MMVD (HANSSON et al., 2005). This variation was also seen in another study that found a maximum variation between three observers of different degrees of experience of 1.0 (LAMB et al., 2000). Twelve patients without heart disease (including boxers and retrievers) also had VHS > 10.7 (LAMB et al., 2000).

Recently, a new measurement has been proposed, very similar to VHS. This uses the manubrium bone, and not the vertebral bodies, as a reference for evaluation of cardiac size and has been named the Manubrium Heart Score (MHS). This study was performed in healthy patients without heart disease (MOSTAFA; BERRY, 2017). No difference was shown between the VHS and MHS in small dogs and one large dog. It was reported that the short axis to long axis ratio was useful in assessing the size and appearance of the cardiac silhouette in normal dogs (MOSTAFA; BERRY, 2017).

However, this paper did not compare this measurement with the echocardiographic examination nor was it calculated in patients with heart disease. Thus, further studies investigating the MHS in patients with heart disease and comparing results with echocardiographic examination are necessary.

The authors believe that this new method might be useful in the evaluation of cardiomegaly, avoiding effects of spinal abnormalities, in patients with heart disease and those with different types of thoracic conformation (MOSTAFA; BERRY, 2017). We hypothesize that there is a positive correlation between this method (MHS) and the echocardiographic examination in dogs with cardiopathies. The objectives of this study were to evaluate the MHS method in dogs with and without myxomatous mitral valve disease (MMVD), to compare the MHS value with echocardiographic measurements in healthy dogs and those with MMVD (LA:Ao; LVIDDN); and to evaluate the effects of observer experience on this measurement

2.2 MATERIALS AND METHODS

Animals

A retrospective, observational and cross-sectional study was carried out using dogs attending the Veterinary Teaching Hospital from January 2015 to December 2016, that had undergone a complete echocardiographic examination in conventional imaging planes as described by Boon, 2011, and had thoracic radiographs in two projections. Radiographs from small breed dogs weighing up to 15kg with or without myxomatous mitral valve disease, which had also had echocardiography, were included. Radiographic examinations were excluded from the study if there were conditions that impeded cardiac measurements, such as pulmonary edema, pleural effusion, neoplasms or alterations in manubrium.

The dogs were divided into two groups for further analysis: group 1 without mitral valve degeneration, i.e. without MMVD, and group 2, the dogs with mitral valve degeneration, that is, with MMVD.

Echocardiographic examination

The cases were selected from the Doppler echocardiographic examination, based on the presence or absence of mitral valve degeneration according to the echocardiographic report. The examinations were performed by the team and supervised by a veterinary cardiologist with 20 years' experience in the area.

X-ray examination

The thoracic radiographs were selected from the database of the Diagnostic Imaging Laboratory and saved in DICOM format. At least two radiographic projections (right lateral and ventrodorsal or dorsoventral) were required, with the lateral projection having the thoracic limbs pulled cranially with the manubrium clearly visible.

All radiographs were initially evaluated by an experienced veterinary radiologist (F.S.J.). Based on the radiological reports for each patient, an experienced veterinarian verified the radiographic quality for inclusion in the study. Cases unsuitable for the measurements were excluded. Samples were randomly separated and arranged using Microsoft Excel® software for later interobserver analysis.

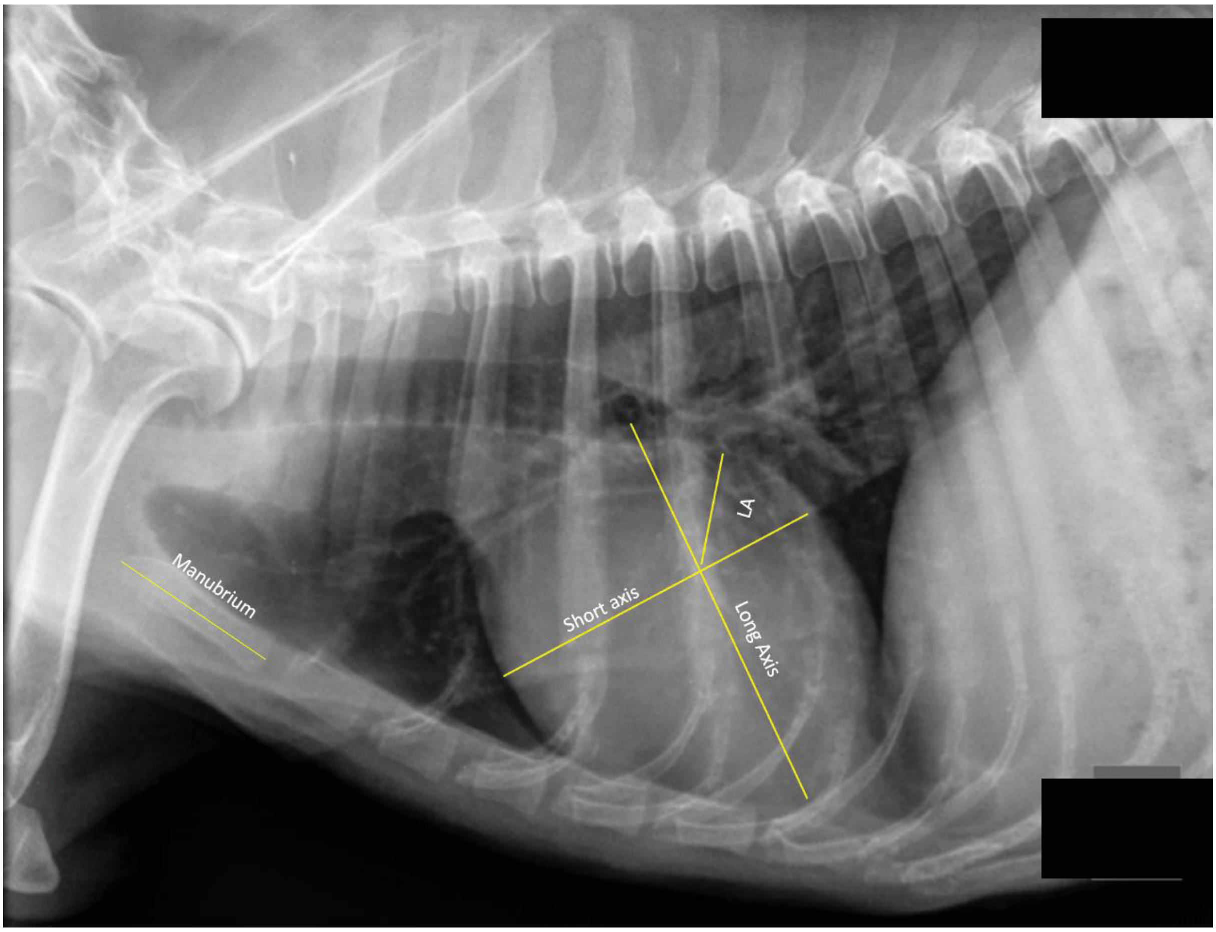
Interobserver study

Three observers with three different levels of experience were selected to perform the radiographic analyzes. The levels were: (1) veterinary radiologist with > 20 years of experience; (2) veterinary radiologist with ten years of experience and (3) veterinarian with three years of experience. The radiographs were randomly selected using Microsoft Excel® software, available in DICOM-type image format for the evaluation of manubrium heart score (MHS). The measurements were tabulated in the same software for later analysis.

Measurements

Manubrium size was measured on the right lateral radiographs from the cranial endfor to the caudal endfor of the structure. The measurement of the long axis (LA) of the heart was obtained in the right lateral radiograph from the length of a straight line running from the tracheal bifurcation to the cardiac apex. The short axis (SA) measurement was obtained from a straight line running at an angle of 90 degrees to the LA, along the longest axis between the cranial and caudal border of the heart. Left atrial size (LAs) was measured by drawing the line at the intersection between LA and SA, with an angulation of 45 degrees to the dorsocaudal border of the heart (Figure 2.1). Measurements of LA, SA, LAs, and manubrium (M) were tabulated in centimeters. The relationships between measurements, such as long-MHS (LA with manubrium), short-MHS (SA with manubrium), LAs-MHS (LAs with manubrium), and overall-MHS (sum of LA and SA with manubrium) were tabulated

FIGURE 2.1 – LATERAL RADIOGRAPH SHOWING MEASUREMENTS OF THE MANUBRIUM HEART SIZE (MHS): LA-LONG AXIS, SA-SHORT AXIS, LA-LEFT ATRIUM LINE MEASURES (LA – LEFT ATRIUM). MHS IS CALCULATED BY ADDING THE LONG AND SHORT AXIS AND DIVIDING BY THE MANUBRIUM.



The signalment data for each patient, as well as the echocardiographic measurements obtained from the echocardiographic reports and the radiographic measurements made by the assessors were tabulated in an Excel table for later analysis.

Statistical analysis

The data were submitted to descriptive statistical analysis to obtain the median, standard deviation and minimum and maximum values using Excel software. Confidence intervals were calculated. All measurements were submitted to the Kruskal-Wallis test to establish statistical significance. Significance was set at $p < 0.05$.

Pearson's correlation was used to determine the correlation of echocardiographic measurements with radiographic measurements. The following correlation scale was used: R-value from -1.0 to -0.7 - strong negative correlation; -0.7

to -0.3 - weak negative correlation; -0.3 to +0.3 - small or no correlation; +0.3 to +0.7 - weak positive correlation; +0.7 to +1.0 - strong positive correlation.

Subsequently, the interobserver analyzes were submitted to the intraclass correlation test to evaluate the degree of agreement among the study observers. To evaluate the level of agreement, the following scale was used: <0 - no agreement; 0 to 0.19 - poor agreement; 0.20 to 0.39 - good agreement; 0.40 to 0.59 - moderate agreement; 0.60 to 0.79 - excellent agreement; 0.80 to 1.0 - almost perfect agreement.

ROC curves were used to evaluate the accuracy of the radiographic measurements and their limit values, and the AUC of each evaluation was calculated. The sensitivity and specificity of the reference values obtained in this test were evaluated. Statistical analysis was performed using Medcalc® statistical software (Belgium, 2018).

2.3 RESULTS

Thoracic radiographic examinations from seventy-nine dogs that had also had Doppler echocardiographic examinations were available. One sample was excluded because the measurements of the heart and manubrium could not be made. In relation to dog breeds, 23 were mixed-breed dogs, ten Beagle, ten Pinschers, seven English Cockers and seven Schnauzers, six Poodles, five Lhasa Apso's, three Dachshunds, two Maltese and two Whippets, and one Brazilian fox, Fox terrier, and Yorkshire terrier.

There were 51 (65%) females and 27 (35%) males. The median, the minimum and maximum values, the standard deviation and the confidence interval were calculated for each radiographic measurement and their relationships to the respective observers (Table 2.1). These averages were also obtained between the observers for each measurement and relationship (Table 2.2).

In the interobserver study, there was almost perfect agreement for measurement of the Long axis, Short axis, left atrium (LAs) and manubrium (M), according to the intraclass correlation test (ICC) (Table 2.3).

The intraclass correlation relationships with these measurements were optimal for Short MHS, Long-MHS, LAs-MHS and Overall-MHS measurements (Table 2.4).

TABLE 2.1 – MEDIAN, STANDARD DEVIATION, MINIMUM AND MAXIMUM VALUE AND 95% CONFIDENCE INTERVAL FOR RADIOGRAPHIC MEASUREMENTS OF THE CARDIAC SILHOUETTE AND MANUBRIUM AND CORRELATION OF THE DOGS FOR EACH OBSERVER. THE MEDIANS WERE SUBMITTED TO THE KRUSKAL-WALLIS TEST TO VERIFY IF THERE WAS DIFFERENCE BETWEEN THE MEASUREMENTS.

Measurements	Median	SD	Minimum	Maximum	95% CI
R1 – Long axis	8.37^{ns}	1.98	4.67	13.89	7.81-8.72
R2 – Long axis	8.52^{ns}	1.97	4.80	14.54	8.14-9.17
R3 – Long axis	8.32^{ns}	1.93	4.67	14.30	7.93-8.96
R1 – Short axis	7.17^{ns}	1.52	4.19	11.56	6.59-7.40
R2 – Short axis	7.31^{ns}	1.55	4.30	11.71	6.67-7.43
R3 – Short axis	7.02^{ns}	1.45	4.12	11.35	6.52-7.28
R1 – Left Atrium	3.03^{ns,**}	1.08	1.44	7.00	2.80-3.22
R2 – Left atrium	2.69$^{ns, ns}$	1.21	1.28	7.32	2.55-3.04
R3 – Left atrium	2.57$^{ns, **}$	0.95	1.13	7.13	2.39-2.73
R1 – Manubrium	2.74^{ns}	0.83	1.15	5.88	2.60-2.92
R2 – Manubrium	2.88^{ns}	0.82	1.63	5.91	2.75-3.09
R3 – Manubrium	2.70^{ns}	0.73	1.49	5.80	2.53-2.83
R1 – Long-MHS	2.95^{ns}	0.53	1.85	4.50	2.78-3.08
R2 – Long-MHS	2.85^{ns}	0.52	1.97	4.85	2.77-2.95
R3 – Long-MHS	2.94^{ns}	0.53	2.14	4.78	2.87-3.14
R1 – Short-MHS	2.46$^{ns, ns}$	0.45	1.81	4.39	2.41-2.61
R2 – Short-MHS	2.35$^{ns, *}$	0.41	1.80	4.15	2.30-2.45
R3 – Short-MHS	2.49$^{ns, *}$	0.41	1.80	3.68	2.43-2.61
R1 – LAs-MHS	1.12$^{**, **}$	0.35	0.70	2.32	1.03-1.20
R2 – LAs-MHS	0.92$^{**, ns}$	0.35	0.53	2.21	0.85-1.04
R3 – LAs-MHS	0.96$^{**, ns}$	0.29	0.46	2.18	0.92-0.98
R1 – Overall-MHS	5.39^{ns}	0.96	3.82	8.89	5.18-5.62
R2 – overall-MHS	5.18^{ns}	0.91	3.95	9.00	5.07-5.50
R3 – overall-MHS	5.43^{ns}	0.91	4.05	8.29	5.28-5.73

^{ns}=not significant at $p = 0.05$. *significant at $p < 0.05$. **significant at $p < 0.01$.
MHS=Manubrium heart score, LAs=Left atrium
R1= veterinary radiologist with> 20 years of experience
R2= veterinarian radiologist with ten years of experience
R3= veterinarian with three years of experience

TABLE 2.2 – DESCRIPTIVE STATISTICS OF THE MEANS OF THE THREE OBSERVERS FOR EACH RADIOGRAPHIC MEASUREMENT OF THE CARDIAC SILHOUETTE OF THE DOGS.

Measurements	Median	SD	Minimum	Maximum	95%CI
Long Axis	8.35	1.95	4.71	14.24	7.84-9.01
Short Axis	7.08	1.50	4.22	11.45	6.56-7.38
Left Atrium	2.76	1.03	1.34	6.95	2.62-2.96
Manubrium	2.75	0.78	1.55	5.86	2.64-2.97
Long-MHS	2.96	0.49	1.99	4.24	2.79-3.04
Short MHS	2.44	0.39	1.85	3.60	2.37-2.60
LAs-MHS	1.00	0.30	0.64	2.24	0.96-1.06
overall-MHS	5.38	0.85	3.94	7.67	5.20-5.55

MHS=Manubrium heart score. LAs=Left atrium.

TABLE 2.3. INTRACLASS CORRELATION (ICC) VALUES AND CONFIDENCE INTERVAL OF ALL CARDIAC AND THORACIC RADIOGRAPHIC MEASUREMENTS IN THE INTEROBSERVER STUDY, IN HEALTHY DOGS AND DOGS WITH MMVD.

Measurements	Intraclass correlation	95%Confidence interval
Left Atrium Line	0.844	0.783 – 0.892
Manubrium Bone Long	0.936	0.908 – 0.956
Long Axis	0.982	0.975 – 0.988
Short Axis	0.988	0.995 – 0.998

TABLE 2.4. INTRACLASS CORRELATION (ICC) VALUES AND CONFIDENCE INTERVAL FOR RADIOGRAPHIC MEASUREMENTS. IN HEALTHY DOGS AND DOGS WITH MMVD.

Ratio	Intraclass correlation	95% confidence interval
Short – MHS	0.738	0.646 – 0.814
Long – MHS	0.774	0.692 – 0.841
LAs – MHS	0.728	0.635 – 0.807
Overall – MHS	0.745	0.651 – 0.821

MHS=Manubrium heart score. LAs=Left atrium.

ROC curves for LAs-MHS and Overall-MHS measurements were made using the LA:Ao echocardiographic measurements and the normalized left ventricular diameter in diastole (LVIDDN) as the classification variables. The area under the curve (AUC) was 0.77 and 0.84, indicating an accuracy of 77% and 84% respectively (p =

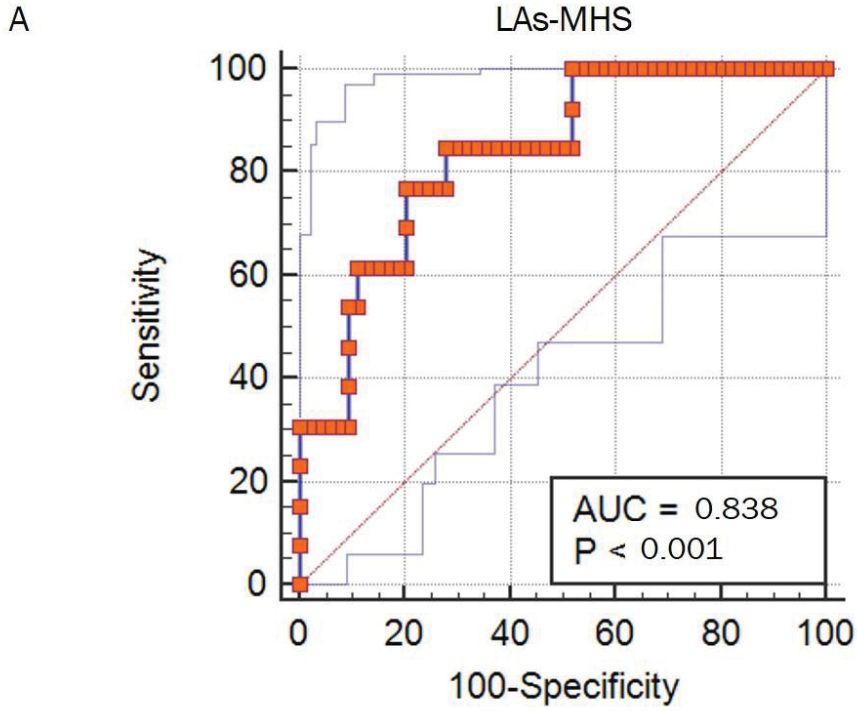
0.006 and $p < 0.001$) in the LAs-MHS relation to LA:Ao and LVIDDN (figure 2.2). With the overall-MHS measurement in relation to LA:Ao and LVIDDN, AUC were 0.61 and 0.68, that is, 61 and 68% accuracy respectively ($p = 0.214$ and $p = 0.059$) (Figure 2.3).

To obtain the cut-off values, the interactive dot diagram derived from the ROC curves was used and the following values were obtained for cut-off, sensitivity and specificity of overall-MHS: LA:Ao on echocardiography exam: 5.94, 59% and 77%, respectively (Figure 2.4A). For the LVIDDN measurement, the values were: 5.97, 62% and 80% respectively (Figure 2.4B). LAs-MHS radiographic measurements compared to LA:Ao, values were 1.13 for cut-off, 77% for sensitivity and 84% for specificity (Figure 2.5A) and in relation to LVIDDN were 1.06 for cut-off, 85% for sensitivity and 72% of specificity (Figure 2.5B).

The results of the Pearson correlation for comparison of the LA:Ao echocardiographic measurement with the long-MHS, short-MHS, overall-MHS and LAs-MHS radiographic measurements were significant at $p = 0.05$ and the values were 0.32, 0.28, 0.31 and 0.65 respectively. The values in comparison of the same radiographic measurements with LVIDDN were 0.28, 0.20, 0.26 and 0.48 respectively. Only the short-MHS value was not significant at $p = 0.05$.

However, Pearson correlation results showed that radiographic measurements have a poor correlation with echocardiographic measurements. Only LAs-MHS had a weak correlation with LA:Ao.

FIGURE 2.2 - IMAGE OF THE ROCS CURVES COMPARING THE LAS-MHS RADIOGRAPHIC MEASUREMENTS WITH THE ECHOCARDIOGRAPHIC MEASUREMENTS LVIDDN (A) AND LA:AO (B).



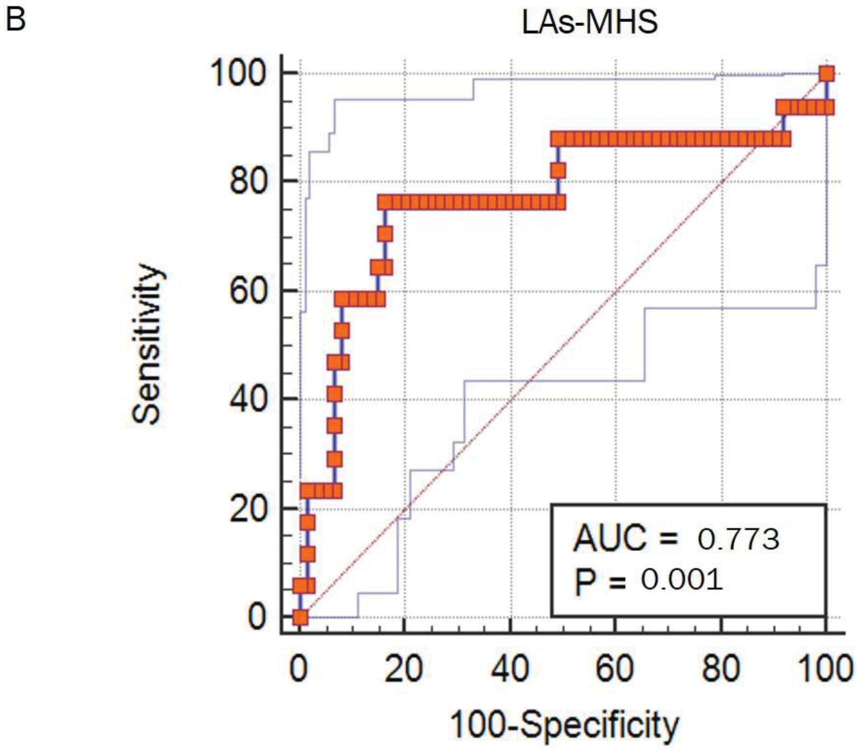
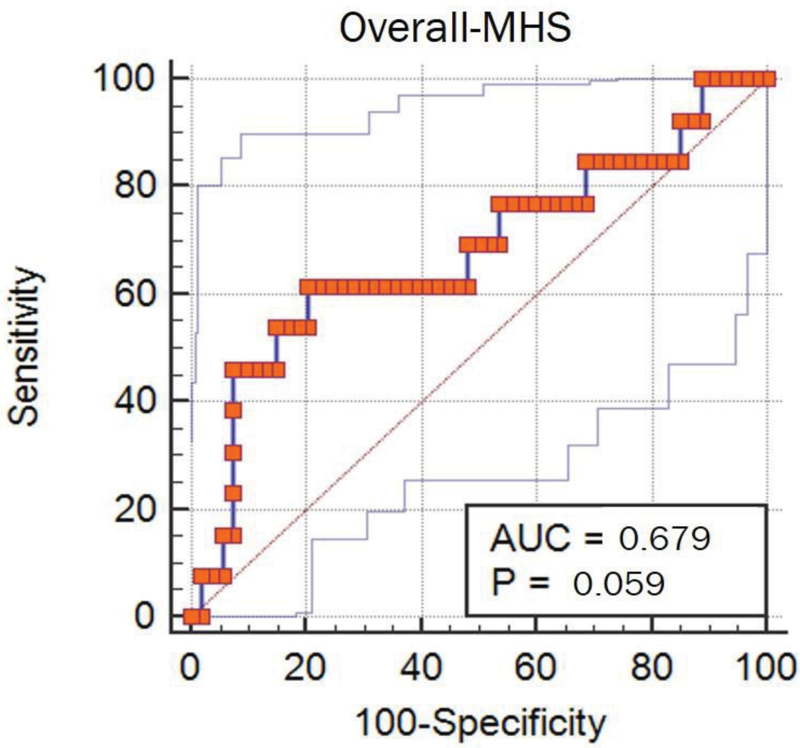


FIGURE 2.3 - IMAGE OF THE ROCS CURVES COMPARING THE OVERALL-MHS RADIOGRAPHIC MEASUREMENTS WITH THE ECHOCARDIOGRAPHIC MEASUREMENTS LVIDDN (A) AND LA:AO (B).

A



B

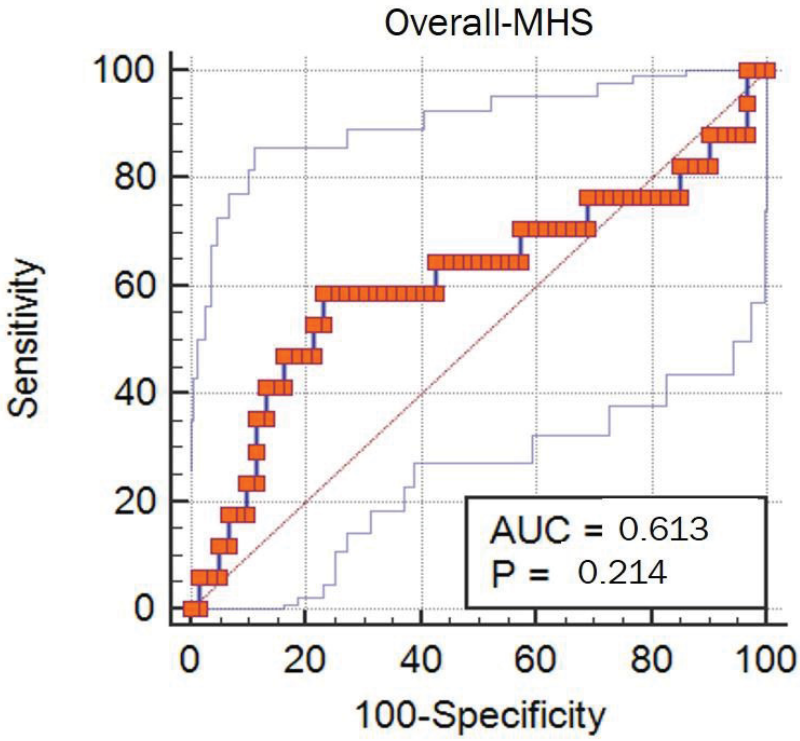


FIGURE 2.4. GRAPHS SHOWING THE CUT-OFF VALUES AND THE SENSITIVITY AND SPECIFICITY OF THE MEASUREMENTS SUBMITTED TO THE ROC CURVE. (A) INTERACTIVE DOT DIAGRAM REFERRING TO THE COMPARISON OF THE OVERALL-MHS WITH THE LA:AO RATIO FROM ECHOCARDIOGRAPHY. (B) INTERACTIVE DOT DIAGRAM REFERRING TO THE COMPARISON OF THE OVERALL-MHS WITH THE LVIDDN OF ECHOCARDIOGRAPHY.

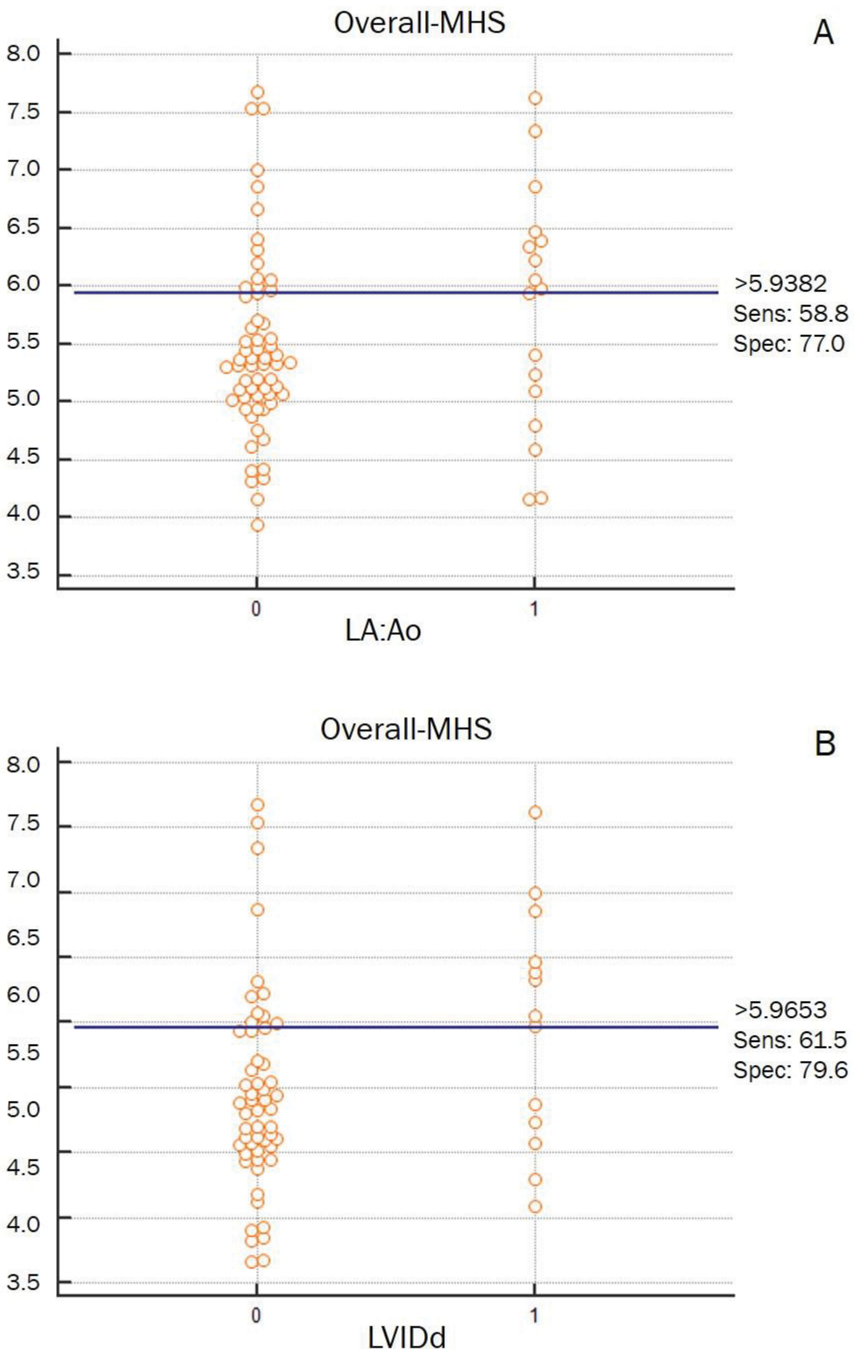
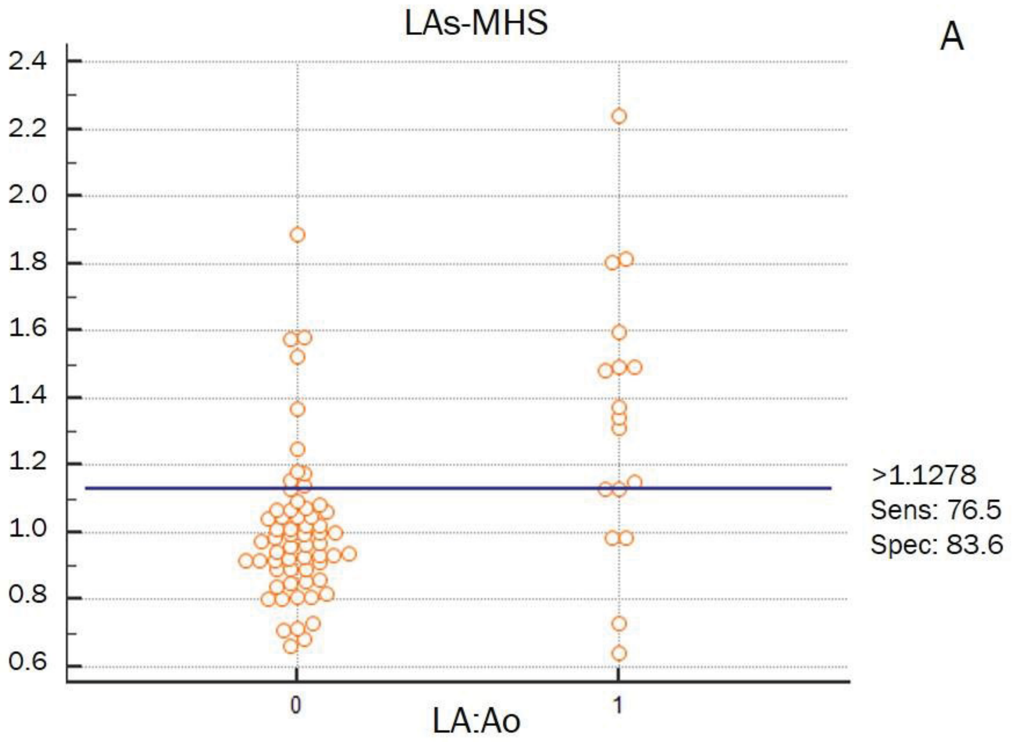
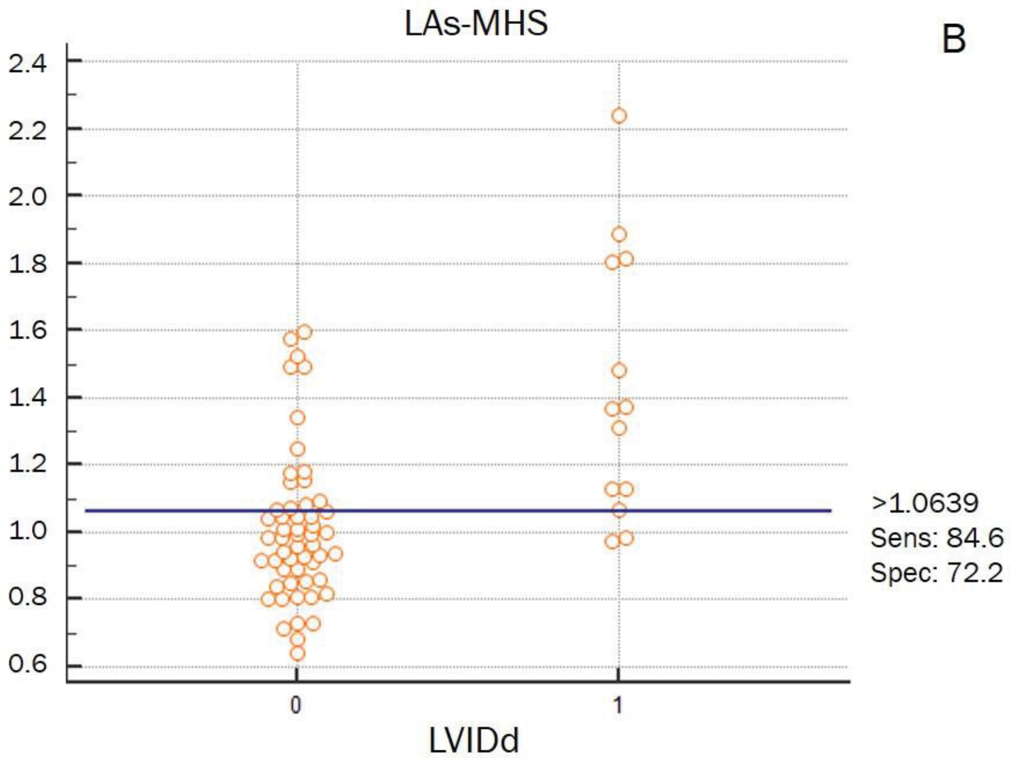


FIGURE 2.5. GRAPHS SHOWING THE CUT-OFF VALUES AND THE SENSITIVITY AND SPECIFICITY OF THE MEASUREMENTS SUBMITTED TO THE ROC CURVE. (A) INTERACTIVE DOT DIAGRAM REFERRING TO THE COMPARISON OF THE LAS-MHS WITH THE LA:AO RATIO OF ECHOCARDIOGRAPHY. (B) INTERACTIVE DOT DIAGRAM REFERRING TO THE COMPARISON OF THE LAs-M.





2.4 DISCUSSION

The manubrium heart score (MHS) has recently been proposed as a good method to analyze cardiac size in thoracic radiography (MOSTAFA; BERRY, 2017) using a method similar to VHS (BUCHANAN; BÜCHELER, 1995). However, unlike VHS, MHS measurements are not affected by vertebral column anomalies and the subjectivity of the measurement of vertebrae and intervertebral spaces (MOSTAFA; BERRY, 2017). However, that study did not include dogs with heart disease, and there was no comparison with echocardiographic measurements suggesting an increase in left atrial pressure and left ventricular size.

In the interobserver study there was almost perfect agreement among the observers for radiographic measurements (Long axis, Short axis, Left atrium and manubrium) and a significant agreement for the long-MHS, short-MHS, LAs-MHS, and overall-MHS. An interobserver study found that there was considerable variance in VHS measurements independent of the observer's experience but dependent on the individual selection of observers relative to the reference points and the transformation of long-axis and short-axis measurements in VHS units (HANSSON et al., 2005).

We showed that there was almost perfect agreement between the observers for the radiographic measurements and little variation between observers of different experience levels. This is probably because the observer needs only to measure the manubrium and it is not necessary to measure the long and short axis of the heart against the vertebrae. Also, abnormalities in the vertebrae and vertebral column (hemivertebra and narrowed intervertebral spaces, for example) may significantly affect measurements made using the vertebrae as a guide in VHS (JEPSEN-GRANT; POLLARD; JOHNSON, 2013; MOSTAFA; BERRY, 2017).

A statistical difference was observed between observers R 1 and R 3 in relation to measurement of the left atrium (Table 2.1). The location of the caudodorsal portion of the left atrium may be difficult to accurately pinpoint for an inexperienced observer. There was also a small difference in the short-MHS measurement between the R2 and R3 observers and there was a statistically significant difference in the LAs-MHS measurement between observer R 1 and observers R 2 and R 3. This may be due to the greater experience of observer R1 facilitating the delimiting of the caudodorsal part of the left atrium.

The ROC curves showed good accuracy for LAs-MHS and accuracy was statistically significant for LVIDDN and LA:Ao, i.e. the echocardiographic measurements used to identify left atrial pressure increase and left ventricular remodeling. However, when compared to the overall MHS, radiographic measurements of LVIDDN and LA:Ao were less accurate and statistical significance was not reached ($p=0.05$).

We showed high accuracy for measurement of radiographic parameters when compared with echocardiographic parameters of left atrial pressure and left ventricular remodeling. However, Pearson correlation showed only weak correlation between these measurements.

A previous study showed an excellent correlation between VHS and the echocardiographic LA:Ao ratio ($r = 0.90$) (NAKAYAMA; NAKAYAMA; HAMLIN, 2001). This was different from our results with our finding of the overall MHS having a poor correlation with echocardiographic LA:Ao ratio ($r=0.31$). This poor correlation and low sensitivity may be associated with delayed remodeling of cardiac structures in dogs with mild regurgitation due to DMVM, such that no cardiomegaly was present.

The cut-off values obtained using the ROC curve comparing radiographic measurements to high pressure left atrial echocardiographic measurements and left ventricular cavity index in diastole can be used to diagnose these changes in patients with MMVD. A cut off of 1.13 for LAs-MHS had a sensitivity of 77% and specificity of 84% (Figure 2.5). A cut off of 5.97 for overall-MHS had 62% sensitivity and 80% specificity (Figure 2.4). Overall-MHS values of 5.1 to 5.5 were reported in healthy small-breed dogs in a recent study. However, these results were not correlated with left atrial echocardiographic parameters (LA:Ao) and cardiac remodeling (LVIDDN) (BOSWOOD et al., 2016; MOSTAFA; BERRY, 2017). These values are lower than those found in our study, which indicates that when overall-MHS is 5.96 there are alterations that suggest a high pressure in the left atrium and remodeling of the left ventricle in dogs with MMVD.

This study has a number of limitations. The low number of cases may affect the statistical analysis, and a larger study, with the separation of cases in relation to the breed of the dogs would be invaluable, since, as for the VHS, there may be differences in MHS between breeds. Inclusion of more cases with high-pressure changes in the left atrium and cardiac remodeling on echocardiography would also be beneficial. Another limitation is the fact that the manubrium must appear on the thoracic radiographs. In some cases, the radiographs do not include the entire manubrium, or the thoracic limbs may be superimposed on this structure, making measurement impossible. The correct positioning of the patient is necessary so that these problems do not occur.

We conclude that the use of manubrium for the evaluation of cardiomegaly in small-breed dogs is an interesting tool for routine use in the clinic as it avoids the effects of abnormalities of the vertebral column on VHS. The overall MHS cutoff value of 5.96 can be used to identify patients who have high pressure in the left atrium and cardiac remodeling. However, there is a need for further studies to validate this methodology in the clinical setting.

2.5 CONFLICT OF INTEREST

No conflicts of interest have been declared.

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CHAPTER 3 - RELIABILITY OF SMARTPHONE-BASED RADIOGRAPHIC INTERPRETATION FOR EVALUATING CARDIOGENIC PULMONARY EDEMA IN DOGS

ABSTRACT

Objective: An intra-observer study to compare the accuracy of radiological diagnosis of cardiogenic pulmonary edema in dogs using two viewing platforms.

Material and Methods: A retrospective cross-sectional study including cases admitted between January 2012 and December 2016. Thoracic radiographs from 121 dogs with and without cardiogenic pulmonary edema were included. The study was divided into two phases and images were interpreted by two observers: a radiologist (R1) and a cardiologist (R2). In the first phase, images were sent in JPEG format for interpretation using a smartphone. In the second phase, DICOM images were interpreted at the standard workstation using a DICOM viewer. ROC curves were generated to evaluate the accuracy of each method of radiological evaluation and Spearman correlation was used to evaluate the correlation between the evaluations performed by R1 and R2.

Results: The accuracy of R1, in determining whether or not a dog had pulmonary edema, was 94.1% (95%CI: 88.3-97.5) for DICOM images and 90.7% (95%CI: 84.1-95.1) for JPEG/Smartphone. The accuracy of R2 was 89.5% (95%CI: 82.6-94.4) for DICOM images and 90.6% (95%CI: 83.9-95.2) for JPEG/Smartphone. There was no statistically significant difference between these evaluation methods. The correlation coefficient for R1 and R2 was 0.815 and 0.761, respectively. There was no statistically significant difference between the 92.5% accuracy for R1 and the 90.0% accuracy for R2 (P=0.2210).

Clinical Significance: Cardiogenic pulmonary edema may be reliably assessed on thoracic radiographs viewed on a smartphone by a specialist to expedite the treatment of patients.

Keywords: Congestive heart failure, Thoracic radiography, JPEG, DICOM, iPhone

CONFIABILIDADE DA INTERPRETAÇÃO RADIOGRÁFICA PELA LEITURA POR *SMARTPHONE* PARA A AVALIAÇÃO DO EDEMA PULMONAR CARDIOGÊNICO EM CÃES.

RESUMO

Objetivo: Estudo intraobservador para comparar a acurácia do diagnóstico radiológico no edema pulmonar cardiogênico em cães utilizando duas plataformas de observação foi realizado.
Material e Métodos: Estudo transversal retrospectivo, incluindo casos admitidos entre janeiro de 2012 e dezembro de 2016. Foram incluídas radiografias do tórax de 121 cães com e sem edema pulmonar cardiogênico. O estudo foi dividido em duas fases e as imagens foram interpretadas por dois observadores: um radiologista (R1) e um cardiologista (R2). Na primeira fase, as imagens foram enviadas em formato JPEG para interpretação usando um *smartphone*. Na segunda fase, as imagens DICOM foram interpretadas na estação de trabalho padrão usando um visualizador DICOM. As curvas ROC foram geradas para avaliar a acurácia de cada método de avaliação radiológica e a correlação de Spearman foi utilizada para avaliar a correlação entre as avaliações realizadas por R1 e R2.
Resultados: A acurácia do R1, ao determinar se o cão apresentava ou não edema pulmonar, foi de 94,1% (IC95%: 88,3-97,5) para imagens DICOM e 90,7% (IC95%: 84,1-95,1) para JPEG / *Smartphone*. A precisão de R2 foi de 89,5% (IC 95%: 82,6-94,4) para imagens DICOM e 90,6% (IC 95%: 83,9-95,2) para JPEG / *Smartphone*. Não houve diferença estatisticamente significante entre esses métodos de avaliação. O coeficiente de correlação para R1 e R2 foi de 0,815 e 0,761, respectivamente. Não houve diferença estatisticamente significativa entre a precisão de 92,5% para R1 e a precisão de 90,0% para R2 (P = 0,2210).
Significado clínico: O edema pulmonar cardiogênico pode ser avaliado com segurança em radiografias torácicas visualizadas em um *smartphone* por um especialista para agilizar o tratamento dos pacientes.

Palavras-chave: Insuficiência cardíaca congestiva, radiografia torácica, JPEG, DICOM, iPhone

3.1 INTRODUCTION

Congestive heart failure is commonly recognized in the small animal clinic. In more severe cases, it can be fatal (ATKINS et al., 2009) usually as a result of cardiogenic pulmonary edema (BAHR, 2018). Cardiogenic pulmonary edema occurs because of elevated filling pressure within the left atrium, causing an increase in the hydrostatic pressure of the pulmonary veins, interstitial extravasation, overloading of the pulmonary lymphatic vessels and consequent accumulation of transudate in the extravascular pulmonary space (MAXIE, 2007). Acquired cardiac diseases, such as myxomatous mitral valve disease, myocardial diseases and some congenital heart disease may lead to pulmonary edema (BAHR, 2018).

Due to the clinical importance and severity of this condition, rapid diagnosis of pulmonary edema is paramount for patient management (BOSWOOD, 2017). Although some limitations and restrictions do exist, radiographic examination is still considered an essential tool in the diagnosis of cardiogenic pulmonary edema in dogs and cats, particularly if there is no access to specialist echocardiography (THRALL, 2018a).

In cardiogenic pulmonary edema, thoracic radiographs usually show a uniform increase in pulmonary opacity, with a predominance of an alveolar pattern, although on initial presentation there may be an unstructured interstitial pattern. The symmetrical, bilateral and caudodorsal distribution of the pattern aid in the determination of cardiogenic pulmonary edema in dogs (THRALL, 2018a), but even in this species an asymmetric distribution can occur, most commonly in dogs with mitral valve insufficiency (DIANA et al., 2009). Another form that helps defining dogs with edema is comparing the pulmonary arteries and veins in thorax X-ray. The pulmonary arteries and veins should typically be approximately the same size (matched). So, if one observes an increase in the diameter of pulmonary veins, that finding could indicate pulmonary congestion and pre-edema (BAHR, 2018).

Teleradiology is increasingly used in routine veterinary practice. Rapid interpretations of images by specialists may aid in the decision-making process, thereby improving the prognosis for the patient. Digital Imaging and Communications in Medicine (DICOM) is the preferred format for interpretation of medical images. Images are usually interpreted by specialists using computers with appropriate reading software and high-resolution monitors (POTEET, 2008). In contrast, Joint

Photographic Experts Group (JPEG) images are more frequently found in smartphone software (DE MAIO et al., 2014). Although it has been speculated that the quality of JPEG images is inadequate for diagnostic interpretation, independent studies conducted by Canada Health Infoway concluded that the irreversible compression in the JPEG/Smartphone format is clinically acceptable (EXNER et al., 2013; NORWECK et al., 2012). To the best of the author's knowledge, only a few studies have investigated the feasibility and reliability of JPEG/Smartphones for the interpretation of medical images. Moreover, no investigation has focused on the diagnosis of cardiogenic pulmonary edema in dogs, which is a known medical emergency, requiring immediate diagnosis.

As in other veterinary hospitals, routine radiographic examinations from our hospital are frequently sent, by the resident on duty, to the experienced radiologist at night and weekends and may be interpreted on portable equipment. The only published study in the veterinary literature on this subject concluded that the reading of radiographic JPEG images on an iPhone® was acceptable for the diagnosis of the gastrointestinal obstructive processes in dogs and cats. However, there were differences between observers that were correlated with the level of individual experience (NOEL et al., 2016).

In this study, the authors hypothesized that the diagnostic accuracy of cardiogenic pulmonary edema in dogs would not be impaired by the interpretation of JPEG images using the small screen of a smartphone as compared to standard DICOM interpretation. Therefore, the objective of this study was two-fold: (1) to compare the accuracy of identification of cardiogenic pulmonary edema in dogs when using two different interpretation resources (JPEG/smartphone format, outside the exam site (off-site) *versus* DICOM format at the place of execution, (onsite)); (2) to compare the diagnostic accuracy of an experienced radiologist and a cardiologist in diagnosing cardiogenic pulmonary edema in dogs.

3.2 MATERIAL AND METHODS

Experimental design

A retrospective, observational, cross-sectional study was conducted to assess the diagnostic accuracy for cardiogenic pulmonary edema in dogs when evaluated using a Smartphone display.

Sample selection

Thoracic radiographs were selected by searching the medical records and PACs at three veterinary teaching hospitals. Cases admitted between January 2012 and July 2016 were included. Inclusion criteria were the radiographic diagnosis of either cardiogenic pulmonary edema or other differential diagnosis such as respiratory, pleural, diaphragmatic and/or mediastinal diseases. Once radiographs exhibiting cardiogenic edema were identified, we further analyzed the patients' medical records to confirm the tentative diagnosis by echocardiographic findings and a positive response to the diuretic therapy. Finally, dogs with respiratory distress as a result of disease other than pulmonary edema were selected based on radiographic findings. One author (F.S.J.) was responsible for the identification and enrolment of cases.

Exclusion criteria included examinations in which the radiographic diagnosis of pulmonary edema could not be confirmed by clinical or echocardiographic examination and there was an inconclusive response to treatment in medical records. Patients that did not have at least two orthogonal projections with adequate patient positioning and exposure were also excluded. Finally, radiographs that did not cover the thoracic inlet, diaphragm, vertebral column, and sternum were deemed unsuitable for this study.

Radiographic imaging protocol

The thoracic radiographs were obtained in any of three X-rays suites (Medicor Budapest, Neo-Diagnomax with 500 mA; EMIC LIMEX 300 mA and CDK Model Diafix 500mA /125kV), and two computed radiography units (Agfa type CR-30X and Fujifilm FCR Prima T2). The technique varied depending on thoracic thickness, body scores and respiratory pattern, but always followed literature recommendations (THRALL, 2018b).

Confirmation of cardiogenic pulmonary edema

Aside from the radiographic characteristics that confirm cardiogenic pulmonary edema, this clinical condition was also substantiated by the documentation, in medical records, of several echocardiographic parameters compatible with cardiac disease. These parameters included surrogates of increased left atrial and ventricular filling pressures such as Left atrium to aorta ratio (LA:Ao)>1.4, mitral E wave-to-isovolumic relaxion time ratio (E/IRVT) >2.5, mitral E wave peak velocity >130 cm/s, diastolic functional classes 3 or 4 (pseudonormal or restrictive pattern, respectively) and mitral E wave-to-mitral annular early diastolic velocity ratio (E:E') >9.1 (OYAMA et al., 2004;

SCHOBER et al., 2010b). Of note, we also selected cases in which medical records indicated either clinical improvement after diuretic therapy or *post-mortem* confirmation of edema.

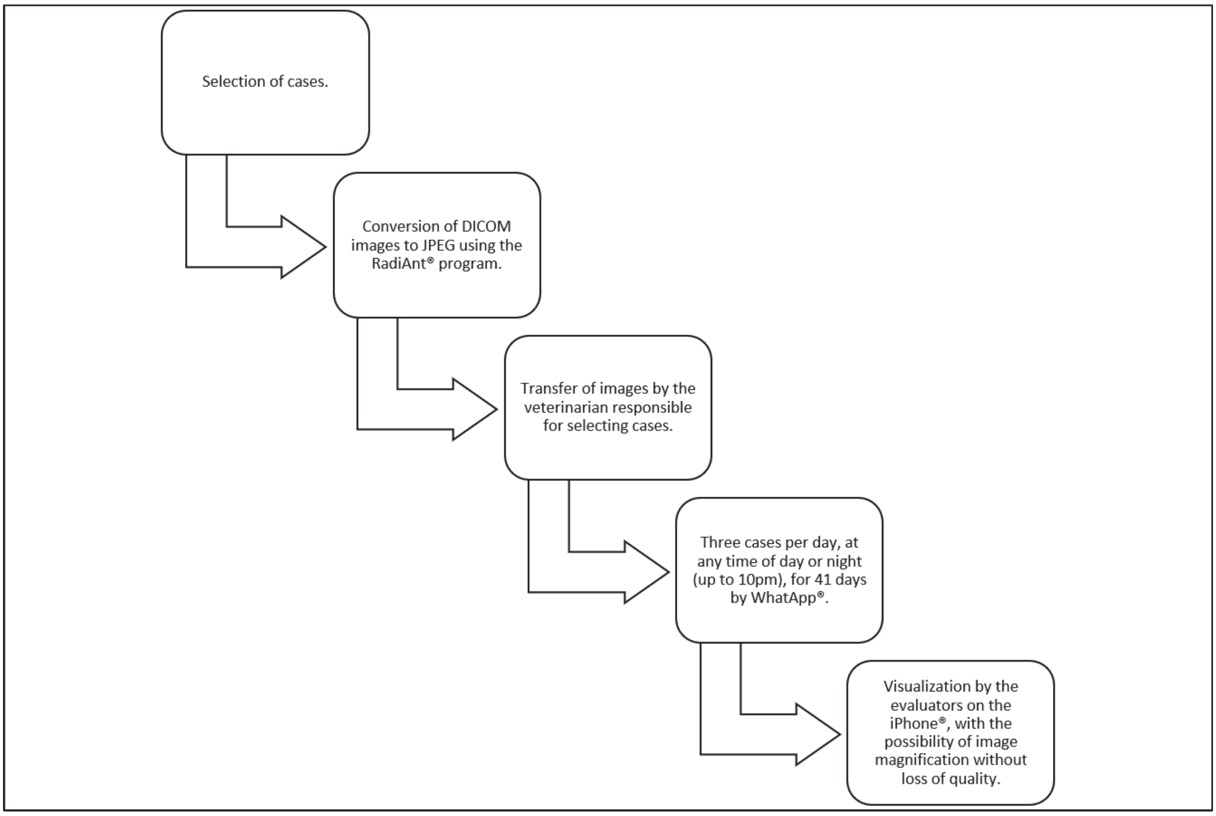
Profile of interpreters, how to send, analyze and receive images:

A single veterinarian (F.S.J) reviewed the medical records and determined category status (i.e. cardiogenic pulmonary edema *vs*. other diseases). All images were interpreted by two observers: a veterinarian board-certified by the Brazilian College of Veterinary Radiology with 20 years of experience in radiology (R1) and a veterinary cardiologist affiliated with the Brazilian Society of Veterinary Cardiology with 15 years of experience in cardiology (R2). Both observers were blinded to details relating to the recorded radiological diagnosis, patient characteristics, and medical history at the time of the study. However, the observers participated in the final diagnosis in approximately 30% of the cases enrolled in the study. Nonetheless, cases were selected at least six months after the initial diagnostic evaluation.

In the first phase of the study, radiographic images were sent in JPEG format to a smartphone (iPhone 6, Apple; 4.7-inch HD display resolution of 1334 x 750 at 326 pixels per inch, 1400:1 contrast ratio, default brightness 504 cd/m^2, pixel pitch 0.08 mm) using WhatsApp, at any time of the day or night (until 10:00 pm). Examinations from three different patients were sent every day for 41 days. Files were converted from DICOM to JPEG format using a desktop computer, and the Radiant software. They were then transferred to the smartphone of the veterinarian responsible for sending the examinations to the interpreters and sent to the examiner by a widely available cross-platform messaging service (WhatsApp®) (Figure 3.1). The observers were required to assess the images as soon as they saw them on the phone. The simulated off-site viewing environment consisted of either an external environment or other parts of the hospital facility with intense lighting.

In the second phase of the investigation, the same examinations were interpreted using an available DICOM-viewing platform (Osirix Lite Pixmeo SARL - Bernex, Switzerland, 2017). An interval of four (4) months was allowed between the first and second phases of the study to avoid interpretation bias. Again, only three cases were interpreted per day at any time. Once the diagnosis had been determined, no further revision was allowed. A total of 126 thoracic digital radiographic examinations were previously selected, however only 121 were interpreted.

FIGURE 3.1 - FLOWCHART OF THE SEQUENCE OF PROCEDURES PERFORMED IN THE FIRST PHASE OF THE STUDY.



The evaluators were asked to state only whether or not cardiogenic pulmonary edema was present. Prior to the study, four test cases were sent to the evaluators to allow familiarization with the study format, as suggested by Noel et al (2016). Each reviewer graded their confidence in their decision to exclude or include a diagnosis of edema using a graded score (Table 3.1). This grade was used to make the comparison between observers and also for comparison with the final diagnosis for each case.

The radiographic characteristics used to define cardiogenic pulmonary edema included signs of cardiomegaly (or at least left atrial enlargement) and pulmonary venous hypertension associated with an increased pulmonary opacification. An increased pulmonary opacity was defined as areas with unstructured interstitial opacification located mostly in the caudal lung lobes, but occasionally progressing to multifocal alveolar lesions obscuring pulmonary vessels. Also, lesions could be either symmetrical or asymmetrical, and mostly located in the caudal lung lobes (BAHR, 2018).

TABLE 3.1 – DESCRIPTIVE TERMS USED TO CLASSIFY THE CASES AS EITHER HAVING OR NOT CARDIOGENIC PULMONARY EDEMA (DICOM /PACS AND JPEG/SMARTPHONE).

Grade	Definition
0	Definitely no cardiogenic pulmonary edema
1	Probably no cardiogenic pulmonary edema
2	Indeterminate
3	Probably cardiogenic pulmonary edema
4	Definitely cardiogenic pulmonary edema

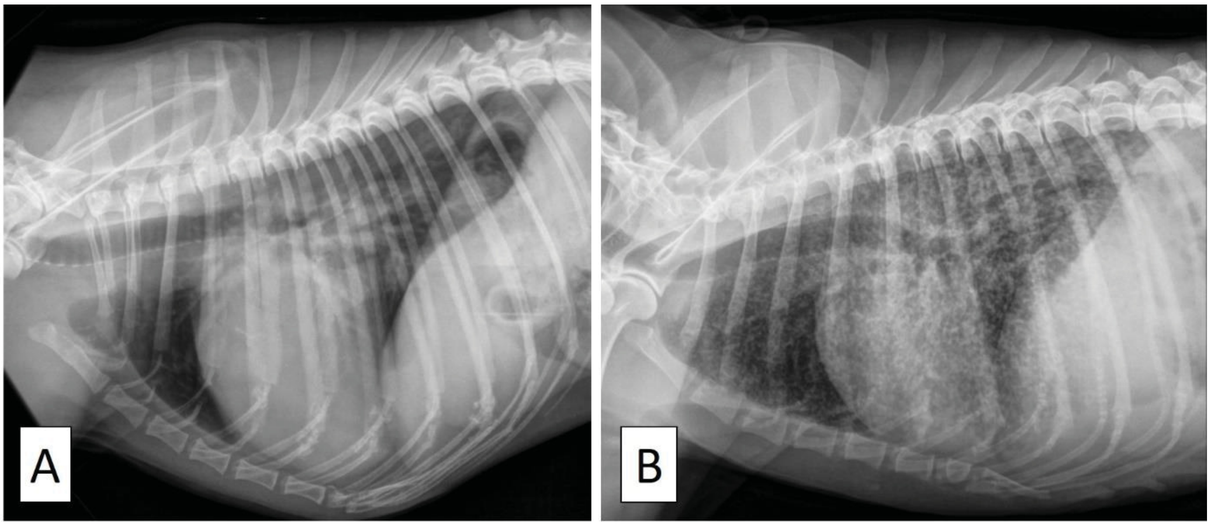
Statistical analysis:

Statistical analyses were selected and performed by one of the authors (F.S.J). Receiver operating characteristics (ROC) curves were generated for each reviewer-imaging interface combination and for each viewing session. The area under the curve (AUC) was calculated to determine accuracy. The AUCs were compared between interfaces and between reviewers (STATA SE, version 14.1, StataCorp, College Station, TX). Spearman's rank correlation coefficient was also performed to assess correlation between ordinal scores from imaging formats and for R1 and R2. Values of $P < 0.05$ were considered significant.

3.3 RESULTS

The sample population consisted of 126 dogs, but five dogs were excluded from the study because of the exclusion criteria. A total of 121 cases were used for analysis; sixty-five (54%) patients were diagnosed with cardiogenic pulmonary edema (Figure 2A), and 56 (46%) were diagnosed with other thoracic diseases. Several medical conditions were represented in the other disease category, including pleural effusion and pulmonary metastasis (Figure 3.2B) (11 each), bronchopathy (4), pulmonary contusion, neoplasm, pneumonia, aspiration pneumonia and pneumothorax (3 each), atelectasis and diaphragmatic hernia (2 each), acute respiratory distress syndrome, bacterial bronchopneumonia, bronchitis, lymphoma, obesity, bacterial pneumonia, fungal pneumonia, inflammatory pneumonia and pulmonary thromboembolism (1 each). Also, two cases with normal thoracic radiographs were included.

FIGURE 3.2 –LEFT LATERAL THORACIC RADIOGRAPH OBTAINED FROM A DOG WITH LEFT SIDED CONGESTIVE HEART FAILURE AND PULMONARY EDEMA, WHICH WAS CORRECTLY CLASSIFIED BY THE OBSERVERS (A). RIGHT LATERAL THORACIC RADIOGRAPHY OBTAINED FROM A DOG WITH MULTIFOCAL INTERSTITIAL NODULAR PULMONARY METASTASIS AND CLASSIFIED CORRECTLY AS “DEFINITELY WITHOUT CARDIOGENIC PULMONARY EDEMA” BY THE VETERINARIANS DURING INTERPRETATION (B).



There were 65 (54%) females and 56 (46%) males. Several breeds were enrolled in the study: Miniature Schnauzer (11), Cocker Spaniel (10), Poodle (9), Dachshund (8), Miniature Pinschers and Whippets (5 each), German Shepherd, Lhasa Apso and Labrador Retriever (4 each), Rottweiler (3), English Bulldog, Chihuahua and Sharpei (2 each) and Bichon Frisé, Blue Heeler, French Bulldog, Cimarron, Dalmatian, Golden Retriever, Maltese, Pitbull, Shih Tzu and Terrier (1 each). However, mixed breed dogs were overrepresented in the study population with 41 individuals.

While the area under the ROC curve (AUC) for R1 was 0.941 for DICOM (overall accuracy of 94.1%; 95%CI: 88.3-97.5), R2 produced an AUC of 0.895 (accuracy of 89.5%; 95%CI: 82.6-94.4). In contrast, when JPEG/smartphones were used for interpretation, R1 had an AUC of 0.907 (accuracy of 90.7%; 95%CI: 84.1-95.1), whereas R2 produced an AUC of 0.906 (accuracy of 90.6%; 95%CI: 83.9-95.2). There was no statistically significant difference in accuracy between viewing methods for the radiologist (p=0.2049) (figure 3.3A) and the cardiologist (p=0.7219) (Figure 3.3B).

The accuracy of the reviewers’ interpretation for JPEG/smartphone was compared to the accuracy for DICOM after a 4-month washout period. The correlation coefficient when the same images were interpreted in different interfaces after four months was 0.815 for R1 and 0.761 for R2. Finally, when all 242 cases from phases 1 and 2 were combined to generate an overall accuracy for each reviewer, no significant difference existed between the 92.5% accuracy for R1 and the 90.0% accuracy for R2 (P-value=0.2210).

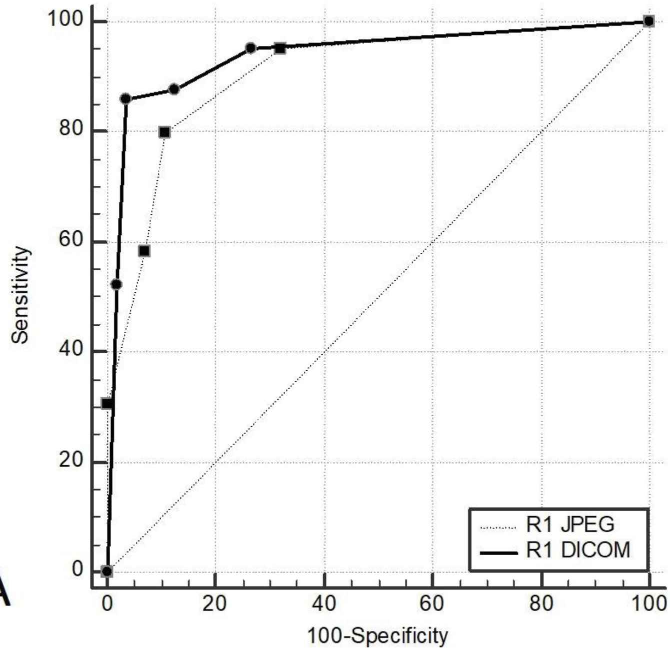
Table 3.2 shows the number of cases that each observer graduated according to the scale of presence or absence of edema and compared with the cases that actually had or had not edema. In 25/65 cases of cardiogenic pulmonary edema the two observers had matched evaluations. For the other cases, diagnosis was consistent between observers in 47/56 of the assessments.

TABLE 3.2 - DIAGNOSTIC PROFILE OBTAINED IN ACCORDANCE TO THE EVALUATION SCALE OF THE PRESENCE OR ABSENCE OF EDEMA USING JPEG / SMARTPHONE AND DICOM / COMPUTER.

	JPEG/Smartphone		**DICOM/Computer**	
	Oedema cases	Non-oedema cases	Oedema cases	Non-oedema cases
RADIOLOGIST				
Category 0 and 1	13	50	8	49
Category 2	14	2	1	5
Category 3 and 4	38	4	56	2
CARDIOLOGIST				
Category 0 and 1	15	52	13	48
Category 2	7	1	5	5
Category 3 and 4	43	3	47	3

Category 0 - Definitely no cardiogenic pulmonary edema
Category 1 - Probably no cardiogenic pulmonary edema
Category 2 – Indeterminate
Category 3 - Probably cardiogenic pulmonary edema
Category 4 - Definitely cardiogenic pulmonary edema

FIGURE 3.3 – RECEIVER OPERATING CHARACTERISTICS (ROC) CURVE CONSTRUCTED TO ASSESS ACCURACY OF THORACIC RADIOGRAPHIC INTERPRETATION BY A (A) CERTIFIED RADIOLOGIST AND (B) AN EXPERIENCED CARDIOLOGIST USING EITHER DICOM OR JPEG/SMARTPHONE. THERE WAS NO SIGNIFICANT DIFFERENCE IN THE AREA UNDER THE CURVE OBTAINED FOR EITHER INTERFACE FOR R1 AND R2 (P=0.2049 AND P=0.7219, RESPECTIVELY).



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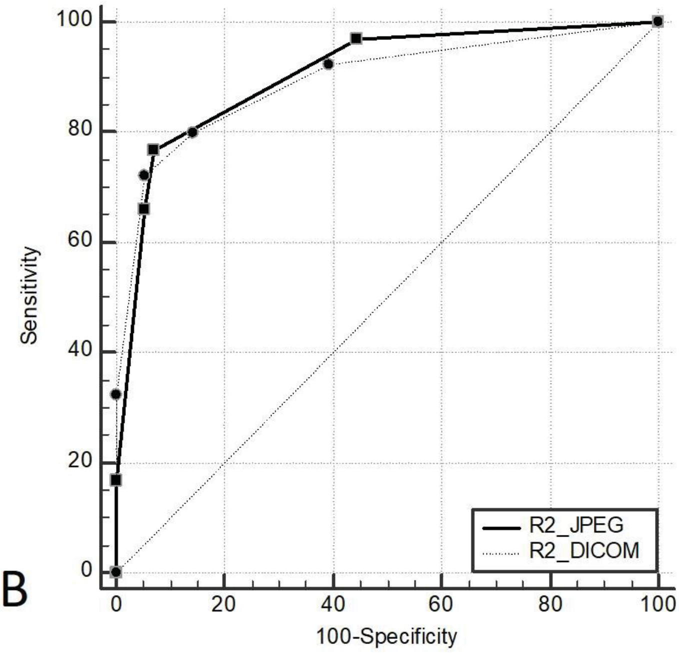

B

3.4 DISCUSSION

In this investigation, we sought to determine whether the interpretation of radiographic images as JPEGs on a smartphone would be as reliable as the DICOM software for accurate identification of cardiogenic pulmonary edema. Our findings supported the hypothesis that accuracy of off-site expert interpretation using a small-screen, handheld smartphone is comparable to the accuracy of conventional, on-site, radiographic interpretation for diagnosis of cardiogenic pulmonary edema in dogs presented with dyspnea. Similar findings have been reported when a smartphone was used in a different clinical scenario (NOEL et al., 2016). This clinical model was chosen as it represents a common out-of-hours scenario at our institution, and most likely occurs in other primary/specialty practices around the globe. Nonetheless, we do not recommend replacement of routine interpretation of radiographs on a standard workstation with a smartphone interface.

In this study, the size of screens used to assess thoracic radiographs had no impact since there was no statistical difference between the two devices. These results were similar to the findings of a study that investigated cases of small intestinal obstruction, and concluded that the size of the viewing screens did not affect the final diagnosis (NOEL et al., 2016). Of note, viewing of JPEG images on a smartphone results in loss of image quality so that some detail could be missed (EXNER et al., 2013; NORWECK et al., 2012). However, the rapid interpretation of whether or not cardiogenic pulmonary edema is the cause of dyspnea can be done without such detail.

Digital radiology makes it simple to present radiographic images in JPEG format and allows for the rapid transmission of large files. Despite the discouragement of the compression and delivery of radiographic images in JPEG (POTEET, 2008) this has become increasingly common in veterinary medicine. Studies such as this are required to explore the limitations of this method of image viewing.

No difference between the evaluators was identified, indicating that acceptable accuracy is achieved when either a radiologist or a cardiologist assesses thoracic radiographs for cardiogenic pulmonary edema. Similar results were observed by Noel et al (2016); however, in that study evaluations were made by veterinarians with varying degrees of experience while in our study the evaluators had equivalent time of training, although in different specialties.

The images used in this work were compressed into JPEGs and transferred to the smartphone by a single author (F.S.J) and, in the first phase, were subsequently sent to the evaluators by social media WhatsApp® to be read. Transforming the DICOM image into JPEG using X-ray viewing programs is a quick and simple procedure. We believe that taking photographs of radiographic images with the smartphone camera might interfere with image quality, therefore impairing diagnostic accuracy.

It was not the aim of these studies to compare this procedure with photographing radiographs. Also, the evaluations in this study were made using a specific type of smartphone (iPhone), and more studies are needed to determine whether other smartphones would provide similar results. The magnification of the image taken while reading the radiographs on the iPhone allowed the documentation of mild changes without loss of image quality.

There was excellent correlation between results obtained by both evaluators when the two interfaces were compared evaluating the same cases four months apart. Although there was a lower correlation for the cardiologist compared to the radiologist, this is probably not related to competence. Instead, the ordinal scale used for the Likert scale may have a reduced correlation, i.e. if a reviewer selected a 0 (definitely not cardiogenic pulmonary edema) for a specific case in DICOM format and four months later selected a 1 (probably not cardiogenic pulmonary edema) for the same case in JPEG format, the correlation would be affected negatively. Nevertheless, the clinical difference between a "definitely no" and "probably no" answer would be minimal.

The numbers of indeterminate cases were similar in both tools (Smartphone and computer) for interpretation (Table 3.2), probably because not every edema case presents with the classical radiography aspects. For instance, dogs with dilated cardiomyopathy may present a bronchial (rather than alveolar) pattern, or an atypical distribution of the alveolar pattern. The atypical distribution is non-symmetrical alveolar, diffuse and/or patchy (THRALL, 2018a). All these characteristics could interfere with the correct interpretation and precise definition of cardiogenic pulmonary edema in thorax radiographs. A way to minimize misinterpretations would be the evaluation of pulmonary vessels. In general, the veins are enlarged in cases of edema. However, their size can change quickly, such as in patients undergoing diuretic therapy, so caution must be taken for this analysis with regards to the final diagnosis (BAHR, 2018). Although a similar accuracy was obtained in this study, we do believe that assessing vessels in the smartphone is more difficult, even with the magnification possibility, as compared to the standard workstation.

Because of these difficulties and problems associated with patient positioning, alternative methods for detection of heart failure are also recommended in the literature, including echocardiography, cardiac biomarkers such as NT-proBNP, and the ultrasonographic assessment for pulmonary edema (Bedside Lung Ultrasound Examination (VetBLUE)) for assessing lung congestion. However, not all of these methods are readily available. Echocardiography and/or VetBLUE can only be performed by an experienced veterinarian (RADEMACHER et al., 2014).

We acknowledge the many limitations of this study. Among them is the absence of testing using a range of smartphones to identify whether screen resolution might interfere with the quality of the radiographic image. Also, there is the possibility that the evaluators remembered the images between examinations although the time interval of four months between the two phases should have minimized this.

In conclusion, the results of this study suggest that experienced professionals can read thoracic radiographs for the detection of cardiogenic pulmonary edema in dogs using smartphones. However, it is more easy to excluded cardiogenic edema from others causes of respiratory distress by smartphones tool. Both evaluators had a high accuracy and there was no significant difference in relation to the diagnosis determined using the standard workstation. Further studies are warranted to evaluate whether different levels of experience and different types of smartphones would change these results.

3.5 CONFLICT OF INTEREST

No conflicts of interest have been declared.

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SCHOBER, K. E. et al. Detection of Congestive Heart Failure in Dogs by Doppler Echocardiography. **Journal of Veterinary Internal Medicine**, v. 24, n. 6, p. 1358–1368, nov. 2010b.

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5. ANNEXES AND APPENDICES

5.1 SCIENTIFIC ARTICLE ACCEPTED FOR PUBLICATION IN THE SEMINA: CIÊNCIAS AGRÁRIAS (CHAPTER 1)

[SCA] Caixa de entrada ×

Prof. Dr. Lucas Alécio Gomes por uel.br
para eu, Stephany, Alexandre, Marlos, Tilde

Prezados autores,

é com enorme satisfação que informamos que seu artigo foi aceito e enviado para editoração de texto.
Obrigo por terem escolhido a revista Semina para submeter o artigo para apreciação.

Atenciosamente, Lucas

Lucas Alécio Gomes, MV, MSc., Dr.
Professor Adjunto de Clínica Médica Animais de Companhia
Chefe da Divisão de Animais de Companhia
Membro da Sociedade Brasileira de Neurologia Veterinária
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5.2 SCIENTIFIC ARTICLE SUBMITTED TO JOURNAL OF SMALL ANIMAL PRACTICE (CHAPTER 3).

Journal of Small Animal Practice - Manuscript ID JSAP-2018-0231.R1 -Mensagem - Email

Responder Responder a todos Encaminhar Arquivo Morto Excluir ...

Journal of Small Animal Practice - Manuscript ID JSAP-2018-0231.R1

KS Kathleen Ann Sanchez <onbehalfof@manuscriptcentral.com>
16:50

Para: fsjojima@gmail.com Cc:fsjojima@gmail.com; marlos98@ufpr.br; tilde@ufpr.br

13-Nov-2018

Dear Prof. Jojima,

Your revised manuscript entitled "Reliability of smartphone-based radiographic interpretation for evaluating cardiogenic pulmonary edema in dogs" has been successfully submitted online and is presently being given full consideration for publication in the Journal of Small Animal Practice.

Your manuscript ID is JSAP-2018-0231.R1.

Please mention the above manuscript ID in all future correspondence or when calling the Editorial Office with questions. If there are any changes in your mailing or e-mail addresses, please log into Manuscript Central at https://mc.manuscriptcentral.com/jsap and edit your user information as appropriate.

You can also view the status of your revised manuscript at any time by checking your Author Centre after logging into https://mc.manuscriptcentral.com/jsap.

Thank you again for submitting your manuscript to the Journal of Small Animal Practice.

Yours sincerely,

Editorial Office, Journal of Small Animal Practice

6. VITA

He holds a degree in Veterinary Medicine from the State University of Londrina (UEL) in February 2003, and has been resident in the Medicine of companion animals with emphasis in the Medical Clinic of companion animals from March 2003 to February 2005 by UEL. Master's degree from UEL in Animal Science, completed in April 2007. He was a substitute professor at the State University of Maringá - Advanced Campus of Umuarama from August 2006 to October 2009. He is currently Professor at the Federal University of Paraná, Department of Veterinary Sciences, Palotina since November 2009.

He teaches classes in Small Animal Medical Clinic, Diagnostic Imaging, Veterinary Clinical Therapy and Veterinary Medicine Intoxication Clinic. Was Director of the Veterinary Hospital of the UFPR Sector Palotina from November 2011 to October 2014. He has been a doctoral student since April 2015.

Below the works published in the doctorate:

JOJIMA, F.S.; LUCINA, S.B.; SANTOS, A.L.; SOUSA, M.G.; FROES, T.R. Use of Measurements from Thoracic Radiographs to Identify High Mean Left Atrium Pressure in Dogs with Myxomatous Mitral Valve Disease. Semina: Ciências Agrárias, 2018 (Accepted).

BRÜLER, B.C.; **JOJIMA, F.S**.; DITTRICH, G.; GIANNICO, A.T.; SOUSA, M.G. QT instability, an indicator of augmented arrhythmogenesis, increases with the progression of myxomatous mitral valve disease in dogs. Journal of Veterinary Cardiology, 2018 (Accepted).

BRÜLER, B.C.; **JOJIMA, F.S.**; DITTRICH, G.; GIANNICO, A.T.; SOUSA, M.G. Instability of the QT interval in dogs with myxomatous mitral valve disease In: 2017 ACVIM Forum, 2017, Maryland. 2017 ACVIM Forum Research Abstract Program. Journal of Veterinary Internal Medicine, 2017. v.31. p.1248 – 1249

WOLF, M.; BRÜLER, B.C.; TULESKI, G. L. R.; LUCINA, S. B.; LOPES, A. P. S.; **JOJIMA, F. S.**; SOUSA, M.G. Assessment of longitudinal systolic function using tissue motion annular displacement in healthy dogs In: 2017 ACVIM Forum, 2017, Maryland. 2017 ACVIM Forum Research Abstract Program. Journal of Veterinary Internal Medicine, 2017. v.31. p.1257 - 1258